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OBSERVATIONS ON ESSENTIAL (HEREDOFAMILIAL) TREMOR

BY

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"A fine tremor, constantly present in typical cases during waking hours, voluntarily controlled for a brief time, affecting nearly all the voluntary muscles, chronic, beginning in very early life, not progressive, not shortening life, not accompanied with paralysis or any other disturbance of nervous function. It resembles to some extent the tremor of paralysis agitans, still more a simple neurasthenic tremor. A most striking clinical feature is its marked hereditary or family type, and its transmission along with other nervous diseases."—*C. L. Dana*, 1887.

ENGLISH neurological literature is almost silent on the subject of idiopathic or essential tremor (tremophilia, Zitterigkeit, tremor simplex) and its clinical variants, the majority of contributions to our knowledge of this subject being in the French or German languages. Merely from a perusal of the writings it is difficult to gain an idea as to the frequency with which essential tremor is encountered. In its nature as a constitutional monosymptomatic peculiarity it can scarcely be regarded as a "disease," and some medical men may never have been confronted with an example. Some cases first come to light when the patient is called up for military service. For every instance coming to medical attention there may be a far greater number in which the victim does not seek professional advice. Moreover, of those cases where a neurological opinion is sought, only a portion are recorded in the literature.

The milder examples therefore pass as a constitutional anomaly which causes little if any disability—a family trait perhaps. Other cases, where the symptom develops comparatively late, may be incorrectly regarded as a manifestation of some clear-cut nervous disease, e.g. Parkinsonism or disseminated sclerosis. When occurring in the aged, it is often looked upon as an integral appanage of advanced years and dubbed "senile tremor."

HISTORY

It is difficult to identify the first reference within the literature of the senile variety of essential tremor, for this type has certainly been noted as one of the hallmarks of old age for centuries. Among the symbolic signs of senility noted in *Ecclesiastes* (XII. 3.) we read—"the keepers of the house

shall tremble," a remark interpreted as referring to tremor of the hands. As regards early accounts of the pre-senile varieties, the problem is less difficult. Sauvages (1768) recorded the case of a pregnant woman who after a fright gave birth to a child afflicted with tremor. This seems to be an instance of an uncommon type of essential tremor, namely the so-called "congenital" variety. The first report of a familial type of tremor would appear to have been made, quite briefly, by Most (1836). Sanders (1872) described a patient with "paralysis agitans" where tremor began at 12 years of age and persisted until the time of death at 66 years. Trousseau (1885) mentioned that "senile tremor" is not necessarily confined to old people and may appear in middle life or even in adolescence, a conception which took many years to root itself within neurological teaching. "On a coutume de dire que cette espèce de tremblement est un effet de la faiblesse que l'âge avancé entraîne avec lui; mais si le fait est vrai en quelque cas, il ne l'est plus d'une manière général; d'une part, en effet, ce tremblement ne s'observe pas necessairement chez tous les vieillards, même très avancés en âge; d'autre part, il se rencontre assez frequemment chez des sujets dans l'âge mûr et même chez des *adolescents*. . . ." Sinkler (1886) also referred to the life-long occurrence of a tremor.

Other early, but brief, references to this type of tremor were made by C. Fernet (1872), Eulenberg (1877), Maragliano (1879), Liégey (1882), West (1885), Charcot (1887), and Predazzi (1887). C. L. Dana (1887) gave the only detailed account of family tremor in the English language and indeed, the first systematic description of the affection. These papers were followed by the contributions made by Haebler (1888), Nágy (1890), Rubens (1891), Débove and Rénault (1891), Raymond (1892), Hamaide (1893), Regnault (1893), Ughetti (1893), Vautrin (1893), Achard (1894), Arnould (1894), Grasset and Rauzier (1894), Brasch (1895), Achard and Soupault (1897), Amore-Bonelli (1897), Mills (1897), and Cestan (1899). The last-named was the first to secure a post-mortem examination upon a patient with this complaint, an opportunity however which proved unilluminating. The story of essential tremor was continued by Iwanow (1899), Graupner (1899) and Minkowski (1903). This century has held fewer isolated case-reports but more serious contributions to the problem, including those by Raymond and Cestan (1901), Mitchell (1903), Kuleke (1904), La Roche (1904), v. Schmaltz (1905), Spiller (1905), Killersman (1905), Neisser (1906), G. Dromard (1908), G. Flatau (1908), Fabricius (1912), and P. Kreiss (1912). The monograph "Das Zittern" by J. Pelnár (1913) is of importance in that it devoted no little space to a consideration of hereditary, essential and senile varieties.

Special reference must be made to a series of papers by the Russian neurologist, L. Minor (1921, 1922, 1925, 1927, 1929), whose views will be discussed in greater detail later.

More recent contributions to the literature of essential tremor are those by A. Roseno (1925), F. Kehrer (1930, 1938), L. Coffé (1927), Noïca (1927), Schenderoff (1927) (a pupil of Minor), R. Hassler (1937), and A. Simon (1931). The last decade has held little new with the exception of two brief but important papers by G. Myle and L. van Bogaert (1940, 1948), and one by E. Katzenstein (1948).

Clinical Manifestations

In the majority of cases, essential tremor appears as a monosymptomatic peculiarity. The subjective complaint is mainly one of tremor to which may be added any mechanical disability that may directly result. Not infrequently the patient misjudges or rationalizes his complaint and seeks medical advice on the score of "nervousness." This is soon found to represent not any psychogenic feature or disorder of mood, but merely the physical manifestation of tremor together with any concomitant anxiety or apprehensiveness.

The age of onset varies within the widest possible limits. The tremor may be present at birth, as in the early case-record by Sauvages. We may in such cases speak of a "congenital tremor." It may develop—rarely—in babyhood or early childhood ("infantile tremor"): or just before or just after puberty ("juvenile tremor"). More commonly it develops in adolescence or early adult life, when the terms "essential tremor" or "idiopathic tremor" are commonly applied. In middle age or later, tremor may develop and may lead at first to the suspicion of an early Parkinsonism ("presenile tremor"). Quite often the tremor does not show itself until an advanced age, when it becomes known as "senile tremor." Although popularly regarded as a characteristic manifestation of senility, it must be remembered that tremor is actually an uncommon physical sign in old age (Critchley, 1931). This observation was made in unequivocal terms by Charcot (1876, 1887), who estimated that out of the 2,000 aged inmates of the Salpêtrière there were no more than about 30 instances of tremor.

Males and females are affected equally.

The course of the affection cannot always be gauged with certitude. As a rule it would seem to be a progressive disorder, in the early stages at any rate. It may be a matter of two or three years before it advances from one segment to another. After an early progression, the symptom may apparently come to a standstill, at least for many years. In later life, however, the tremor may rather suddenly become aggravated, and thereafter progress with some rapidity. Additional neurological features may at this stage now make their appearance for the first time.

It is rare, though not unknown, for a remission, or a period of betterment to occur, once the tremor has made its debut. Such spontaneous improvement has been noted by Kreiss (1912) in one of his cases, though

he does not make it clear how long the remission lasted. Improvement also took place in the following family, in the case of two brothers:

P. C., male, aged 38, had suffered from tremor of both hands since adolescence. It varied considerably in intensity, and seemed to be improving until the age of 34 when it grew much worse again. At the age of 37 the tremor also spread to affect the right leg. His mother, aged 64, has had tremor for 40 years. His younger brother also suffered from tremulous hands, the tremor at one time being very marked; he too gradually improved. The patient, P. C., developed at the age of 34 years symptoms which proved to be due to a meningioma of the left fronto-temporal region.

The tremor generally appears first in a hand and forearm. Sometimes the right and left limbs are simultaneously affected but more often one side is involved before the other. Rarely, however, does the tremor remain entirely restricted to one limb for long. The common sequence is from one hand to another over a period of two or three years and thereafter for the tremor to remain more marked in the segment originally involved. It is rare, but not unknown, for the tremor to spread from one hand to the ipsilateral lower limb and thereafter to constitute a hemitremor. More usually the tremor spreads to involve the head and neck or some other part of the cranial musculature. This cranial involvement is diagnostically important, especially when—as sometimes is the case—the head, neck or jaw are implicated first. Such a progression would be unusual, for example, in Parkinsonism, but it is characteristic of one of the modes of development of idiopathic tremor.

Within the region of the head and neck, tremor may occur at the occipito-atlantoid articulation, or in the masseters, the facial muscles, the eyelids, the external muscles of the eyeballs, the extrinsic and intrinsic muscles of the larynx, the tongue and the palate.

Trunkal muscles are rarely involved except perhaps in the very late stages. The diaphragm may also be shown skiagraphically to be the seat of a tremor.

Following Flatau we may recognize certain common groupings of musculature involved by tremor:

hands only;
hands and lips;
arms, head, larynx;
hands, lips, eyelids, tongue;
arms, tongue;
hands, head;
arms and legs;
ipsilateral arm and leg;
arms, legs, head, larynx;
arms, jaw, tongue;
arms and neck;
arms, legs, tongue;
hands, nystagmus of eyeballs.

Not only does the tremor vary in its site but it differs from one case to another in its clinical characters. In the case of the hands, it ranges from a fine and rapid oscillation of the fingers, up to 12 per second, to a much slower type of tremor of wide amplitude (4 per second). The former type bears a superficial resemblance to thyrotoxic and psychogenic tremor, while the latter type recalls a Parkinsonism. The tremor may appear while the limb is at rest (static tremor or rest tremor), and may be temporarily inhibited during the execution of a voluntary act. In other cases the tremor seems to be present at rest so long as the hands are outstretched, but ceases when the hands are supported adequately on a table. A third type of case is reminiscent of cerebellar disease in that a crescendo augmentation occurs during a voluntary movement (intention tremor).[1] Rarely there may be no trace of tremor while the patient is at mental or physical repose, but as soon as he comes under emotional tension: if he believes he is being watched: or if he concentrates his attention: or if uncomfortably cold: or if muscular tonus is raised, tremor appears. Flatau has suggested the term "intermittent tremor" in such cases.

Typically, no tremor occurs during sleep, though both Vautrin and Iwanow have noted its continuance during sleep. In the waking state the tremor varies in intensity according to a number of factors, both intrinsic and extrinsic. Almost always the tremor is increased under emotional stress—often conspicuously so—as when the patient is nervous or embarrassed. Hence arises the common complaint that the patient finds difficulty in signing his name when under observation, although he may experience no awkwardness in writing when alone. Not only does emotional duress increase a tremor but it may also cause it to spread so as temporarily to involve other previously unaffected segments. The willed attempt to control a tremor may lead to an exacerbation.

Fatigue tends to increase the tremor, though, on the other hand, Klucke has found the disability greatest during the morning after a night's rest.

Thermal environments of either extreme are apt to augment the tremor: usually cold is more nocuous than warmth in this respect, though the opposite occurred to an extreme degree in one of my cases. An intercurrent painful malady located near the site of the tremor (e.g. an acute arthritis) intensifies the tremor. The taking of alcohol is of interest in this connexion. Some patients find that a heavy dose of spirits will temporarily check the tremor and this factor has appeared only too often to have served as an excuse for habits of intemperance. Some hours after an

[1]Though the terms intention tremor and action tremor are usually applied synonymously, de Jong (1926) has utilized the latter in an unorthodox fashion. Believing that rest tremor, intention tremor and action tremor are three different conditions, he nevertheless held that transitions between the first and third are often seen.

alcoholic excess, however, the tremor becomes increased and is associated with the physical and mental malaise of a hangover. Tea, coffee, and tobacco have also at times a temporarily aggravating effect. Démange laid stress upon hunger as a deleterious factor, and noted that cases with tremor were always better immediately after a meal. This observation does not seem to have been corroborated by any of the subsequent writers upon this subject, though it applied strikingly to one patient in my series. The act of sexual congress or even erotic excitement has been noted as causing an increase in the tremor. In the case of intentional types of tremor of the hand, the involuntary movement may seem to augment, the finer the manipulation being carried out. When one speaks of a tremor as

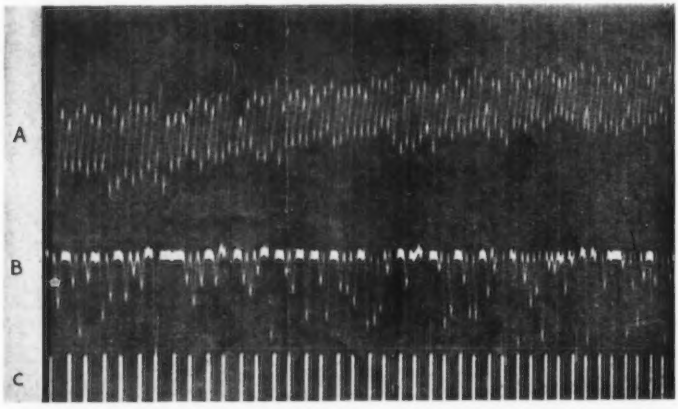


FIG. 1.—Record of a familial essential tremor of the right forearm in a man aged 69 years (arm resting). A. Flexion—extension movement of the middle finger. B. Side to side movement at the wrist. C. Time marker. 66 beats per minute.

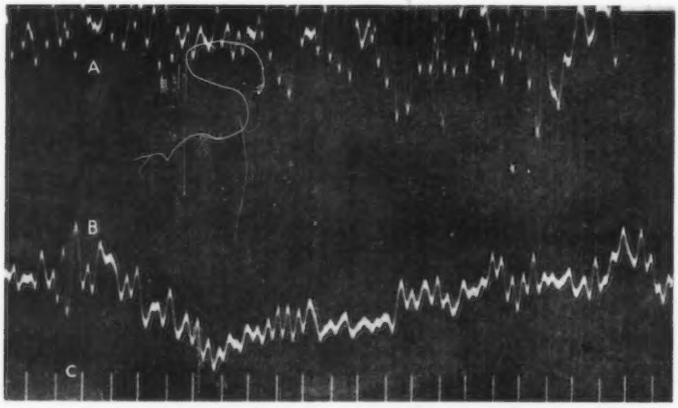


FIG. 2.—Same patient; arm unsupported.

"increasing," one refers of course to a change in the amplitude and not the rate of the oscillations.

The tremor when affecting the upper limbs consists in repeated alternate contraction through a small range of antagonistic muscle-groups. The rate varies from about three to twelve per second (*see* figs. 1 and 2). As already mentioned, the finer types of tremor are reminiscent of thyrotoxic states; the coarser types are usually accentuated by action and recall the tremor of disseminated sclerosis; intermediate types resemble Parkinsonian states.

When the head is affected the tremor may consist in a vertical or nodding movement (*tremblement affirmatif*), or a horizontal one (*tremblement negatif*). Occasionally the movement is an oblique one. When the mandible is affected, the patient seems to be constantly chewing. In cases of essential tremor of the face there may occur a repetitive grimacing especially of the lips or of the chin. One of Démange's patients was dubbed "old rabbit face" on this account. In the rather uncommon cases where the legs are involved, the maximum movement is usually proximal and consists of alternate flexion and extension movements of small amplitude at the hip-joint. An unusual case of senile tremor of the legs, in a patient of Professor Schuster of Berlin, was earlier described by Critchley (1931):

> Male, aged 80, had gradually developed a tremor of the left leg, five or six years previously; later, the right leg became similarly afflicted. Both legs were rigid, especially noticeable as he walked. When he was seated the right leg was held out in a posture of full extension. Knee and ankle jerks were sluggish on the right and unobtainable on the left. Both plantar responses were flexor in type. The arms were normal. Speech was lisping and imperfectly articulated. The tremor of the legs consisted in coarse rotatory movements of the whole limb, especially marked in the thigh. The movements were greatly aggravated by both passive and active movements of the legs.

Articulation may be affected by the presence of tremor though it may be difficult to assign the defect to any particular muscle-group. Tremor of the muscles of the larynx, the lips and tongue and of the diaphragm, may severally or in combination be responsible for the characteristic quavering type of speech.

The tremor not unnaturally constitutes a handicap in that it may interfere with the smooth and co-ordinated execution of a delicate movement—as in articulation. However, the tremor is far less of a disability than one might expect. Even in the intention type of essential tremor, an effort of will may intervene so as to inhibit the trembling for a moment or two. Consequently the existence of tremor does not preclude certain manipulative professions or occupations. One has witnessed at work a surgeon who was a victim of essential tremor; he was able to control the oscillations long enough to make a movement of precision with his scalpel or to ligate a bleeding point. Minor described essential tremor in a watch-

maker. Another patient in my series was a highly skilled artificer. Haebler's patient was an accomplished billiards player. Except for movements successfully carried out during the short-lived spells of inhibition, movements of a protracted sort are distinctly hampered. Thus the handwriting of a patient with essential tremor shows tremulous features, with angularity of what should be a rounded letter. The pathological nature of the script becomes easily recognizable. It differs from the handwriting of a patient with Parkinson's disease in that there is no micrographia (*see* fig. 3).

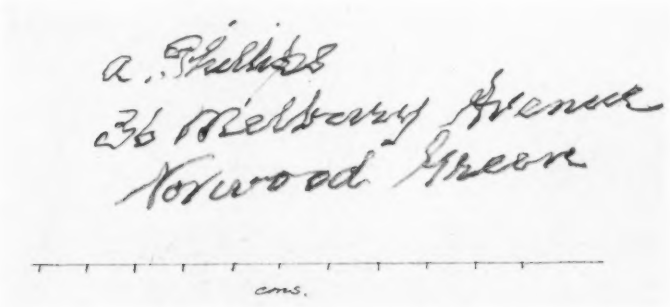


FIG. 3a.—Handwriting of a patient with essential (heredofamilial) tremor. Note the absence of micrographia.

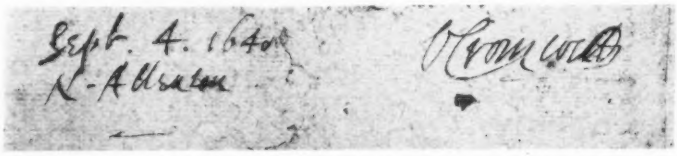


FIG. 3b.—Signature of Oliver Cromwell (who is said to have suffered from a familial tremor of the right hand). Written 1640 (aet. 41) and reproduced by gracious permission of His Majesty the King.

FIG. 3c.—Signature of Oliver Cromwell written 1658 (aet. 59) and reproduced by courtesy of the Public Record Office. (Ref. S.P. 18/180, fo. 150). In 1655 the Venetian Ambassador wrote that . . . "I have found Cromwell somewhat haggard in appearance and looking in not quite good health . . . the hand holding his hat was trembling."

Occasionally, other involuntary movements may accompany the tremor, e.g. choreiform contractions of the face (Graupner), or of the head (Débove and Rénault); choreo-athetosis (Achard); facial twitching (Schmaltz); spasmodic torticollis (Mills, Minkowski).

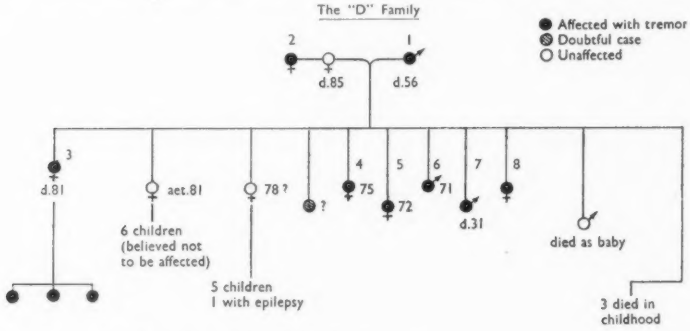
The foregoing are the main "positive" features of essential tremor. It is perhaps advisable to emphasize that there is no alteration in muscle-tonus; no real ataxia; no change in the reflexes; and no sensory disturbances. There are none of the other physical signs of a Parkinsonian syndrome, such as poverty of movement, slowness of movement, an attitude of flexion, or a damping-down of the various so-called "associated" movements.

Genetics

One of the most striking features of essential tremor is its frequent familial occurrence, as originally noticed by Most over 120 years ago. The genetic details are still somewhat obscure, however, and it is probable that more than one type of inheritance may be concerned. In most families the affection is transmitted as a dominant.

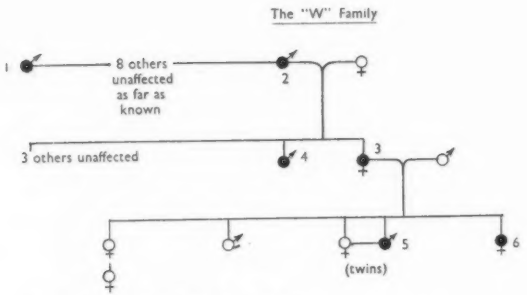
In Dana's family A, no fewer than 45 members were proved to be involved. Out of the family recorded by Coffé there were 15 cases in four generations. Pintus published the pedigree of a Sardinian family with tremor; out of 200 members belonging to seven generations, 16 cases of tremor were traced.

Two personal family trees may be reproduced, not so much as a typical but as an extreme instance of hereditary occurrence of tremor:



1 Is believed to have been "shaky"
2. Suffered from well marked tremor of the head.
3 Was very shaky....had "St. Vitus' dance of the head" Her 3 children (sex unknown) were slightly tremulous.
4. Tremulous when hurried or excited.
5 Paralysed since childhood (?poliomylitis) very tremulous.
6. Tremor most of his life: worse since 63 years of age
7. Tremor Died in India at 31 years.
8 Tremor of head.

Table 1.



1 Tremor of head in late life. D. aet. 87
2. Tremor of both hands; eventually unable to feed himself. D. aet. 84.
3 Tremor of hands; slow, coarse, much exaggerated by volitional movement. Onset at 30.
4 Tremor of hands; slowly progressive. Sudden exacerbation at 55 or 60. D. aet 75.
5 Slight tremor.
6. Fine, rapid tremor of hands; onset as a schoolgirl. Now aet 35

TABLE 2.

In the case recorded by Dromard (1908) both parents were tremblers, besides the patient and one of his two brothers. In Hamaide's case also, both parents were tremulous. The same circumstances apparently occurred in family D. One generation may be skipped (Dana); or even two (Raymond and Hamaide). Kehrer, after studying the pedigrees of Minor's cases, asserted that the tremor was neither sex-linked, nor sex-restricted, nor sex-controlled. He believed, however, that a "crossed heredity" took place twice as often as a "homonymous heredity."

Most of the family trees which contain sufficient data, show that the phenomenon of anticipation is well marked—as in the Family W. (Kreiss, Liégey, Habler, Rubens, Raymond, La Roche, Schmaltz). Hence we may find the rather striking but characteristic state of affairs whereby a tremor appears in successive generations as a senile tremor, and then a presenile, an adult, an adolescent, a juvenile, and finally, a "congenital" variety.

MORBID ANATOMY

From the literature it seems that only a few instances have been recorded of a pathological study of essential heredofamilial tremor.

Cestan (1899) examined the morbid anatomy of a complicated case in which hereditary tremor was one of the manifestations. The patient, his mother, his two brothers, and his son, had all been afflicted with tremor. In addition he suffered from myoclonic twitches, and from epilepsy, like his mother. At the age of 10 years he gradually developed a pes cavus deformity in the right foot; at the age of 46 years a similar appearance developed in the left foot. This neurological picture was regarded—rather unconvincingly—as an instance of progressive muscular atrophy following

poliomyelitis. From the pathological picture it was not possible to identify any changes which might be held responsible for the longstanding tremor.

Bergamasco (1907) had under observation a man of 65 who had shown an intention tremor of his upper limbs since the age of 50. Examination also revealed nystagmus, and a slow scanning dysarthria. The author regarded the case as one of disseminated sclerosis. Histological study of the central nervous system failed, however, to reveal any abnormality. Consequently the diagnosis was changed to one of "senile" tremor.

O. Maas (1914) gave a clinical description of two cases of essential tremor. Eight years later during the discussion which followed Minor's paper at the Berlin Society for Neurology and Psychiatry, Maas mentioned that one of these patients had died and that Lewandowsky had failed to find any histological abnormality within the central nervous system.

R. Hassler (1937) was able to examine the brains of two brothers. The first, an alcoholic who died at the age of 71, had shown for many years a gross rotatory tremor of the head to the left, and an intermittent tremor of the limbs exaggerated by movement. His brother, who died at 80, had shown a coarse tremor of the hands, choreo-athetotic movements of the feet, and hypotonus. Their other brother and their father had been similarly afflicted. In the former case, Hassler found a great reduction in the number of small cells of the dorsal part of the caudate and putamen. In the other case he discovered a similar reduction in the small cells of the striatum, with an *état précriblé* of the dorsal two-thirds of the putamen and caudate nucleus, and less marked in the lateral nucleus of the thalamus and centro-median nucleus of Luys. There was a pallor of the Purkinje cells with circumscribed lamellar atrophy.

Myle and van Bogaert (1940) observed a case of hereditary tremor which was abolished by an apoplexy sustained 4½ weeks before death. Pathological study demonstrated (1) a clear cut cellular outfall in the Purkinje cell layer, and to a lesser degree in the pallidum, together with an increase in the amount of astroglia which was laden with brownish-grey pigment; (2) a fibrillary gliosis of the superior cerebellar peduncle, of the white matter of the cerebellum, of the pallidum, and of the lateral nucleus of the thalamus; and (3) an undue cellular gliosis in the dentate nuclei, and of the roof nuclei, with scattered pigmentation. Such alterations were bilateral. There also occurred a vascular lesion within the superior part of the internal capsule involving the hind part of the caudate nucleus.

The same authors (Myle and van Bogaert, 1948) were also afforded the opportunity of examining the brain of another case. A woman, dying at 74 years, had suffered from a tremor of the head and hands since the

age of 16. There was no family history of tremor. As she grew older the patient, who had always been a dullard, developed paranoid ideas of reference. At autopsy, cerebral changes were found which did not resemble their previous case. The putamen and caudate presented a typical and extensive *état criblé*, with some cellular outfall and gliosis. The lateral nucleus of the pallidum was rarified with a moderate cellular and fibrillary gliosis, extending into the fields H_1 and H_2. Considerable rarefaction existed within the bulbar olives. A cellular reduction was found in the Purkinje layer of the cerebellum.

It cannot be claimed that our knowledge of the pathology of essential tremor is much advanced by these reports. There is not a great deal of correspondence between the few records available and it is, moreover, not easy to disentangle the microscopic changes which might be ascribed to involutional factors. Myle and van Bogaert also referred in the first of their two papers to the pathological findings in cases of hereditary tremor in animals (guinea-pigs, American white mice, fowls, domestic mice, pigs). Here the changes are mainly strio-pallidal in situation, and are more reminiscent of those found in Huntington's chorea.

The Tremor Diathesis

Although some of the earlier writers were clear as to the nosological nature of essential tremor, it was many years before it was realized generally (1) that senile tremor is not identical with Parkinson's disease; (2) that senile tremor is actually only a late manifestation of hereditary tremor; and (3) that essential tremor and hereditary tremor are one and the same condition.

An interesting conception was advanced by Minor in a series of papers with regard to the ætiology of essential tremor. Two peculiarities impressed Minor in his studies of families affected by tremor, namely, the advanced age which many of the members attained, and secondly, the large size of the families. Upon these points, Minor raised the conception of a *status macrobioticus multiparus*, characterized by the triad of tremor, longevity and fecundity. The longevity was a feature of both of those who showed tremor and of their unaffected relatives. Out of nine families with tremor, Minor found that the siblings numbered 9 (twice), 10 (twice), 11, 12, 15, 16, and 19. One family comprised 15 children in one generation, 16 in the next, and 18 in the third. The pedigree which contained 19 siblings in one generation was made up of 15 living offspring and 4 abortions. It is interesting to recall that about ten years earlier, Pelnář had commented on the large number of relatives who constituted the pedigrees of these cases of familial tremor.

As regards longevity, Minor found, out of 50 cases afflicted with tremor, the following age-incidence:

Age	*Males*	*Females*	*Total*
70	10	3	13
71–80	15	8	23
81–85	4	1	5
85–90	—	2	2
91–95	1	2	3
96–99	—	1	1
100	2	—	2
105	1	—	1
Totals	33	17	50

Attempts were made, rather unconvincingly, to compare the age-incidence of tremor-patients with the general population. Thus in Minor's series of tremblers there was one person aged 80 or above to every 14·5 case-record; this proportion is about eight times the expected figure, for—if the 1876 census records for France can be taken in comparison—there was one octogenarian to every 116 persons.

Of Minor's total series of 683 relatives, there were two centenarians, and one individual aged 105; that is, a proportion of one very aged person to 227. This figure may be contrasted with the incidence of centenarians in the general population. Thus in France out of a total of 40 million inhabitants there were 150 centenarians, a proportion of one to 266,666. In 1890 there were 21 centenarians in London out of a total of 4 million, the ratio here being 1 to 190,476.

This interesting idea of a status macrobioticus has often been quoted in relation to essential family tremor, but not necessarily critically. Minor's statement has been noted but not examined. Kehrer (1930) indeed, while apparently accepting Minor's opinion, went so far as to make the point that the two properties of longevity and fecundity are often to be noted in other heredofamilial affections of the nervous system. Langevity has also been mentioned as commonly found in association with Parkinsonism (Mendel; Mendel and Lewy; Glorieux; Oppenheim). Kehrer also considered the relationship of fecundity and of twinning in association with various hereditary nervous disorders other than tremor.

Pintus (1938) failed to corroborate Minor's conception of longevity and fecundity. He studied these points in the 200 members of the family he had previously recorded, and found no difference between the prolificacy of this family and of the general local population. The longevity of the members of his family proved to be slightly less than the general population.

In recent times, Katzenstein (1947) has broadened somewhat the conceptions of a status macrobioticus multiparus. In a series of seven families

in Switzerland, afflicted with tremor, the author found that all the families, save one, were characterized by exceptionally high intelligence, professional attainments, and placid temperaments. Others have elaborated this idea, believing that these individuals are of lusty virile personalities, who both work and play hard, eat heavily and drink deeply. Essential tremor has certainly been observed among well-known personages of high intelligence, e.g. the neurologist Babinski. According to Besenval, quoted by Frey, Louis XV was afflicted with an "idiopathic" tremor of the chin muscles, which always appeared in circumstances of emotional excitement.

This is an idea rather at variance with that expressed by many other writers who have regarded family tremor as more of a degenerative disorder both in a neuropsychiatric and a sociological sense. Raymond was perhaps the first to associate essential tremor with psychical degeneration. Achard suggested that the condition should be called "névrose trémulante."

Even earlier, Dana had quoted details of three families, in one of which alcoholism, insanity, eccentricity and epilepsy, featured prominently, as well as tremor. But, be it noted, several other members of this family showed "intelligence and mental activity much above the average." It is also of interest to notice that Dana found that most of the members of this family lived to an advanced age. In his second pedigree, where an uncle and two nephews were afflicted with tremor, one was also addicted to alcohol.

Raymond, who wrote his first paper on essential tremor in 1892 and continued to study and discuss the subject for years afterwards, always insisted that the condition was associated with a neuropathic stock. Brasch (1895) mentioned that one of his patients with family tremor was neurotic, while a step-sister was afflicted with mental disorder. Labbé (1897) recorded hereditary hemitremor in association with epilepsy, athetosis, and degenerative stigmata.

Alcoholism was also mentioned as a significant feature in the pedigrees of cases of tremor by Liégey, Vautrin, La Roche, and by Flatau. The last-named recorded in his family M. that the grandfather, father and two sons were all heavy drinkers. But Flatau hastened to state that tremor is a rarer disease than alcoholism, and he quoted the family reported by Nágy where, in a family showing both alcoholics and tremblers, few of the alcoholics were actually affected with tremor.

Aside from inebriety, Flatau was impressed by the neuropathic taints in the families with tremor. He mentioned data from earlier writers; the occurrence of nervousness (Regnault); of emotivity (Nágy and others); of anxiety states (Rubens, Schmaltz); intolerance towards alcohol and tobacco (Brasch). Flatau did not wish to overemphasize these features.

Pointing out that serious mental disorder is a rarity in tremor-families, he concluded that a neuropathic taint may play a part, though not a prominent one (". . . eine gewisse, wenn auch nicht hervorragende Rolle . . ."). The great majority of the cases, he said, offer no traces of a psychical *Entartung*.

Pelnář believed that the personalities of patients affected with essential tremor were characterized by irritability, anxiety, shyness, eccentricity, irresolution, irascibility, tics, and other neurotic, hysterical or psychotic traits.

In recent years, M. Mussafia (1947) believed there was a connexion between tremor, tics, stammering and dementia. All, he believed, occurred in neuropathic families, and were pathologically interrelated.

Psychotic states occasionally co-exist, depression being the commonest example. But Flatau believed that "severe" nervous disorder was rare in tremor-families.

A. Simon (1930) recorded an unusual case where a 50-year-old male patient had for years suffered from a fine tremor of the head and a coarser tremor of the hands. He had been rejected from the German Army in 1902 on that account. His father and grandfather had been similarly afflicted. For many years he had also been a prey to manifold neurotic symptoms, with anxiety, *folie de doute*, agarophobia, and various obsessional traits. In addition he was liable to peculiar states, brought on by emotion, when he would stand or lie immobile . . . "as if paralysed . . ." From the author's description one cannot determine whether these episodes represented cataplectic attacks or bouts of affective hypertonus.

The association with "congenital nystagmus" is of interest. Minor, and also Kehrer, debated whether tremor of the head of congenital or early appearance, may not in itself be associated with a congenital (often hereditary) nystagmus, which in turn may have been due to albinism, refractive errors, optic atrophy, or some other ocular defect. One should draw a clear distinction between a combination of tremor of the limbs with familial nystagmus (which must be very rare), and the not uncommon familial syndrome of tremor of the head and nystagmus (Nettleship, 1909, 1911). Tremor and nystagmus have been associated within the same family tree by Predazzi (1887), Schmaltz (1905), Flatau (1908), Kreiss (1912), as well as Kehrer himself (1930). More recently there is on record a family of nystagmus-myoclonus described by Lenoble and Aubineau (1902), characterized by tremor, nystagmus, intellectual changes and stigmata of degeneration. These last-named included facial asymmetry, uterine infantilism, visceral inversion, *pied creux*, colour-blindness, strabismus, anisocoria, deaf-mutism, and enuresis. These authors identified four types of nystagmus in childhood: (1) isolated, essential

nystagmus; (2) essential nystagmus combined with various neurological signs (anisocoria, facial asymmetry); (3) essential tremor with specific nervous features (increased reflexes, clonus); and (4) a familial type of nystagmus, associated with tremor and perhaps other neurological manifestations. van Bogaert and E. de Savitsch (1937) have recorded familial occurrence of nystagmus, tremor of the head and arms, a flexed posture of the head on the trunk and loss of automatic arm swinging movements. Out of 109 members of this family, 40 were affected. A great variety of clinical variants was noted among these, such as, for example:

Isolated tremor	12 examples
Tremor of head, nystagmus...	11 examples
Tremor of head, nystagmus, dystonia of neck	2 examples
Nystagmus, rhythmic movements of arms	1 example
Tremor of head and arms, nystagmus, dystonia of neck	6 examples

In addition, various psychiatric features were often associated, e.g. epilepsy (three times), psychopathy (twice), mental defect (three times), and severe psychoses (twice).

The authors drew attention to a pedigree studied in Sweden by Verlander (1931), where since 1600, 300 persons have been afflicted with involuntary movements of the tongue and chin, disordered speech, tremor of the trunk, and altered gait:

> A case of non-familial essential tremor of the hands, of cerebellar type, in a man aged 19, associated with slight mental defect and bilateral macular degeneration, was kindly shown me by my colleague, Dr. D. Brinton.

Amongst other purely physical manifestations that have at times been recorded in association with familial essential tremor, we may mention torticollis (Kehrer), club foot, maldevelopment of the phalanges, weakness of the face and external ocular movements, hyperhidrosis (Kreiss), and deformity of the fingers (Schenderoff).

At this point one may refer to the occasion when Raymond and Thaon (1905) demonstrated to the Société de Neurologie de Paris, two pheasants afflicted with a generalized tremor. The birds were male and female and both were the offspring of consanguineous parents. The previous covey had consisted of delicate birds with whitish, discoloured plumage but no tremor. There was no trace of paralysis or of inco-ordination though all movements were hampered by the fine vertical tremor of the body. During repose the tremor was less evident, but on excitement and on movement it became enhanced. As they walked they seemed to be shivering with cold. This tremor was congenital in that it was apparent as soon as they were hatched. Both birds were feeble and were sterile. Raymond and Thaon regarded the condition as comparable with the essential hereditary tremor in man, and they proposed to sacrifice the birds in order to study the morbid anatomy. No subsequent communication can be traced, however.

In the literature there are accordingly two contrary viewpoints, namely that essential tremor is a sort of "macrobiotic" manifestation; and, conversely, that it is a "degenerative" disorder associated with a neuropathic family taint. Despite the size of the literature there is still an inadequate documentation. More family pedigrees are needed, and in each case closer study is required. The conception of "macrobiosis" is a difficult one to maintain on the one hand, while on the other hand many of the features that have been regarded in the past as degenerative taints, cannot be reconciled with modern opinions.

"Macrobiotic" features may well exist within the same pedigrees as various "microbiotic" traits. We see this association well illustrated in the very considerable family tree of the Bures-Connecticut stock with Huntington's chorea, as described by Vessie (1932), Davenport and Muncey (1916), and others. As Dana asserted in his paper on hereditary tremor ". . . it is associated with other neuroses or psychoses, such as insanity, inebriety, and epilepsy, and also with examples of unusual talent or intellectual vigour. And it illustrates the fact that a neuropathic taint in a family may develop as a disease, or as some brilliant mental endowment. . . ."

The Nature of Essential Tremor

Perhaps the most interesting aspect of the problem of essential tremor devolves around a consideration of the nature of this condition. A life-long monosymptomatic affection can scarcely be regarded as falling within the province of a morbid entity, any more than any other inborn and inherited peculiarity of physique or colouring. Kreiss (1912) believed that essential tremor was a kind of exaggeration of physiological tremor, and that it formed a part of a "general inferiority (Minderwertigkeit) of the nervous system." Kapus (1947) suggested that the inherited forms of tremor were an "intermediate grade between the physiological and pathological forms of tremor." Ignorant of any pathological correlation, Minor (1922) surmised that essential tremor was perhaps ". . . not a disease, but a functional expression of a cerebral anatomical malformation . . ."

A pathological entity would be suggested could it be shown that essential tremor is not so much an inborn deviation, as an incomplete variety or clinical fragment of some well-defined neurological disorder. Here again Minor had asked the question ". . . can it be a forme fruste of some other disease characterized by tremor . . .?" There is, as a matter of fact, a certain amount of evidence to support such a conception, in a few cases at any rate. Kehrer seems to have held the opinion that essential tremor mostly represents a part of a complex hereditary disposition.

Were this the case, we would, as clinicians, expect to find from time to time (1) families in which some members show essential tremor and others

some well-established disease entity; and (2) "complicated" cases of essential tremor with additional physical signs; and (3) patients whose essential tremor later in life increases in distribution and intensity, and becomes associated probably with the development of other signs.

Indubitably, all the foregoing phenomena have been encountered and the literature holds a few brief allusions on this point. Two neurological affections come up for discussion in this connexion, namely Parkinson's disease, and presenile cerebellar degeneration.

Thus detailed history-taking may reveal that a close relative had been a sufferer from paralysis agitans. This association has been noted specifically in several cases in my series as in the following:

Male, aged 75, had noticed shaking in the right hand for about one year. The tremor was of the typical senile variety, and there was no evidence of Parkinsonism. One of the patient's brothers had had tremulous hands all his life, his present age being 71; another brother, now aged 65, had shown symptoms of paralysis agitans for 17 years. Two second cousins had also suffered from tremulous hands. (Critchley, 1931.)

Whether this occurrence is statistically significant cannot be affirmed. Paralysis agitans is, of course, a not uncommon malady, and chance may well account for its cropping up within a pedigree of heredofamilial tremor. Brasch (1895) and others, have referred to such, though his family was of interest in that the tremor was inherited from the paternal side of the family, while the Parkinsonism occurred in a maternal aunt. It would obviously be of far greater significance if a family history could be adduced containing *more than one* case of paralysis agitans. A search of the literature has so far failed to disclose any such occurrence.[1]

The second point concerns the possible association of essential heredofamilial tremor with one or more signs of an extrapyramidal order enhancing the superficial resemblance with a Parkinsonian state. No such case has as yet been clearly described, except for the van Bogaert–de Savitsch family.

Lastly there is the possibility that a patient suffering from long-standing essential heredofamilial tremor may in later life assume the clinical manifestations of a Parkinsonian syndrome. This phenomenon certainly has been encountered but again one cannot exclude a coincidental development of paralysis agitans.

In the following case-record there is an association between a long-standing tremor, a familial incidence of tremor, and the subsequent development of paralysis agitans.

A. M., male, aged 63 years, had always been tremulous. His father and both his brothers had also suffered from a similar tremor of the hands. At the age of

[1]This problem has also been discussed by R. J. Vakel ("Parkinsonian manifestations arising in a Parsee family with essential, primary, or familial tremor," *Ind. Med. Gaz.*, 1943, **78**, 594); and by H. Mjönes ("Paralysis agitans. A clinical and genetic study." Munksgaard, Copenhagen, 1949).

60 years, the left hand had become more tremulous and the left leg also became involved. His medical adviser at that date recognized that he was developing Parkinson's disease. At 63 years of age he showed a very characteristic picture of paralysis agitans.

Neurological opinion has for years vacillated in its conceptions of whether a relationship exists or not between paralysis agitans and senile (or essential) tremor. Certainly J. Parkinson (1817) in his monograph on "The Shaking Palsy" distinguished strictly between the two conditions. It is doubtful whether other writers followed his lead, however, either disagreeing with Parkinson, or else being ignorant that a distinction had been made by him. Seventy years later we find Charcot protesting against those writers who ". . . sous prétexte sans doute d'unification philosophique, d'esprit de synthèse . . ." were claiming that paralysis agitans and senile tremor were one and the same.

Thereafter it was generally believed that the two types of tremor were ordinarily distinct entities; and that senile (and essential) tremor could be distinguished by the complete absence of the so-called hypertonic-akinetic manifestations of pallidal disease. Nevertheless, the idea gradually developed that exceptional cases may be recognized as forming a sort of linkage between essential tremor and Parkinsonism. That some sort of relationship may exist between essential heredofamilial tremor and Parkinson's disease was indeed suggested by Gowers. Thus in his Manual (1888) he wrote ". . . the brother of a third (patient with paralysis agitans) was said to have suffered all his life from a peculiar non-progressive tremor . . ." Concerning senile tremor he also wrote ". . . There is not, however, any sharp line of demarcation between the two affections, and it is difficult to say in which category some cases should be placed . . ." And later, ". . . it is doubtful whether this senile tremor is essentially different from paralysis agitans. Some cases are met with of a character intermediate between the two affections . . ." Pelnář, writing of senile tremor in 1907 said ". . . Pathogenetisch und vielleicht auch ätiologisch steht er der Parkinsonschen Krankheit nähre, indem er einen Teil ihres Gesamtbildes ausmacht . . ." E. Gelma (1913) recognized a so-called "rhythmic oscillatory tremor" intermediate between the senile and the Parkinsonian varieties, which, he believed, formed the opposite poles of a single morbid entity. Gradual transitions connected these three types of tremor, he believed, all being based upon analogous cerebral changes. Noïca (1927) also speculated whether there was an actual structural relationship between hereditary tremor and paralysis agitans.

The following case is of interest from this standpoint:

A highly intelligent Judge had developed tremor of the hands at the age of about 40-45 years. His mother had been similarly afflicted but had lived to the age of 89. No disability resulted until he reached the age of 63 when he became more tremulous, slow in movements and, later, more confused and helpless. When

examined he was found to show a marked dementia with double incontinence; tremor of the arms, lips and mandible; a Parkinsonian attitude and facies; bilateral forced grasping. The blood pressure and arteries were normal. He was regarded as a case of Jakob's disease and he died a few weeks later at the age of 64 years. No autopsy was performed.

Even more interesting, unless of course coincidence is to be regarded as the explanation, is the association of a post-encephalitic Parkinsonism with a family history of tremor. The possibility that a constitutional diathesis towards tremor may have been precipitated by an encephalitis can neither be denied nor refuted.

A Greek woman, aged 35 years, showed a mild Parkinsonian syndrome, a right-sided tremor having been present for about 10 years. The patient's mother, then aged 70, had been afflicted with tremor of the hands for some years, while the maternal uncle (now aged 85) showed a side-to-side tremor of the head.

The problem is even more interesting when one deals with tremor in its relation to the presenile cerebellar atrophies. In the first place the two conditions may be co-existent with the same family. Secondly, a patient may have for years shown tremor of the hands; but later in life other disorders—of imbalance, stance, gait—may develop, so that the picture of a delayed cerebellar atrophy develops. We are still unaware whether the association is a fundamental one or not, for we do not know anything of the morbid anatomy of such cases. It is possible that the clinical resemblance is merely superficial and without a basis in morbid anatomy. This must be regarded as improbable, however.

A man, aged 73, without any family history of tremor, developed a tremulous right hand at the age of 60. After 12 years or so this became worse and he also became depressed and irritable. Examination revealed a constant titubation of the head and a static tremor of both hands, more especially the right, grossly increased by volitional activity. His speech, too, was tremulous. The gait was normal and there was no trace of ataxia. Knee-jerks were present though the ankle-jerks could not be elicited. Plantar responses were flexor in type.

This case, like the following, may well be regarded as a transitional one between the tremors and the cerebellar atrophies.

A woman aged 76 began to show a tremor of the head at 62 years—a condition which had been present in her mother and her sister. A few weeks before being examined she developed an explosive type of dysarthria. The tremor had recently spread to involve the muscles of the trunk including the diaphragm. There was a cerebellar type of inco-ordination in the left upper and lower limbs. Both ankle-jerks were sluggish, the plantar responses being flexor. There was a good deal of emotivity with a tendency towards pathological laughter.

In a recent paper (M. Critchley and J. G. Greenfield, 1948) the opinion has been expressed that in some cases an essential heredofamilial tremor might represent a forme fruste of one of the presenile cerebellar atrophies and, more particularly, olivo-ponto-cerebellar atrophy. Hanhart had previously suggested that essential tremor might perhaps exist as a "partial" Friedreich's ataxia. In the families he had studied, he found

many siblings whose condition resembled this form of hereditary ataxia. P. Schuster (1922) also suggested that transitional cases occur between senile tremor and late Friedreich's ataxia, or olivo-ponto-cerebellar atrophy.

Clinical studies of essential tremor and the meagre data afforded by morbid anatomy cannot be said to advance our conception as to the physiology of tremor in general.

While the idea that tremor may be the result of some irritative mechanism—as in the *tremor coactus* of the resting state—has long been regarded as untenable, the present view is, and has been for many years, to conceive tremor as a release phenomenon. There has been an increasing tendency to regard tremor as the "normal" mode of functioning of certain cerebral mechanisms, which is kept in check with greater or lesser success by other activities. That this inhibitory function may be feebler in some individuals than in others, is shown by the tendency for tremor to appear with undue ease in certain physiological circumstances, e.g. fatigue, cold, emotion. This experience leads to the conception of a "trembling inclination" to use the words of de Jong.

It is tempting to regard essential heredofamilial tremor as an instance of an unmasking of an inherent property of neurocellular activity, as the result of some constitutional defect in the usual controlling mechanism. Along such lines we may perhaps understand why tremor should at times antedate the development of such involutional disorders as paralysis agitans and olivo-ponto-cerebellar atrophy, where tremor is a conspicuous feature.

Whether this constitutional defect rests upon a pathological basis cannot yet be affirmed. The cases recorded by Hassler and by Myle and van Bogaert indicate that if there is a foundation in morbid anatomy, the site of the lesion is probably not circumscribed or even consistent. This would be in accord with the experiences of the experimental production of tremor under physiological conditions. Bucy (1944), for example, believed that tremor could follow an interruption of a circular controlling mechanism embracing the precentral motor cortex, the locus niger, globus pallidus, the fore-part of the central thalamic nucleus, and back again to the cortex. On clinical grounds, however, many would prefer to include the cerebellar nuclei within the sphere of the tremor-controlling mechanism. Minor, for example, spoke of a quadrilateral region of the brain wherein one could place the lesions which were likely to be followed by tremor: this area embraced the pallido-striatum, the thalamus, the corpus Luysii, the cerebral peduncles, the dentate nuclei, and the upper part of the pons. S. A. K. Wilson (1925) also spoke of tremor being normally controlled by an "involuntary" prespinal centre or centres at the

general level of the corpus striatum, cerebellum and mesencephalon. Walshe (1929) expressed the opinion that tremor in paralysis agitans is not more than the exaggeration of a normal phenomenon and that it possibly represents the emergence of a normal cortical rhythm through defect of lower level mechanisms. Quite recently A. A. Ward, W. S. McCulloch and H. W. Morgan (1948) have produced a Parkinsonian type of tremor in monkeys by making destructive lesions below the basal ganglia, and within the mesencephalic and pontile tegmentum. There was no correlation between the electro-encephalographic records and the electromyograms of the tremor. The authors believed that the tremor was the expression of the uninhibited rhythmical activity of the reticular formation.

The anatomical zone mapped out by Minor, Bucy and others, as being significant in the genesis of tremor, recalls a somewhat similar region which has been associated with the phenomenon of palatal nystagmus. A triangle connecting the red nucleus, the dentate nucleus and the inferior olive, has been shown by Guillain and Mollaret (1935) to include all the known sites of morbid change noticed in recorded cases of palatal nystagmus. In the circumstances it is a matter of surprise that essential tremor and palatal nystagmus are not combined more frequently. Two points of distinction need to be stressed. In the first place palatal nystagmus is essentially a pathological manifestation, developing usually in middle life or later, and resulting from an unmistakable focus of disease. Secondly, the involuntary movements of the palate (pharynx and larynx) belong to the category of a myoclonus rather than a tremor. The chief points of distinction between myoclonus and a tremor are the consistency of the former and its continuance during sleep. In these respects the palatal movements must be regarded as myoclonus, but it is interesting to recall that van Bogaert and Bertrand (1928) in their study of palatal nystagmus, believed that myoclonus and tremor were very closely related.

Nevertheless, there are a few case reports which indicate that a palatal nystagmus may be associated with a tremor of the head, of the neck, or of the limbs (Steward, 1903; Freystadtl, 1928; Lhermitte, de Massary and Trelles, 1933; and Guillain and Thurel, 1933). In the following personal case, there was an interesting association between tremor, palatal nystagmus and a senile cerebellar syndrome:

F. J. W., male, aged 71 years, had complained for ten years of tremulousness and increasing difficulty in walking. For seven years he had experienced difficulty in talking. The family history was negative. Examination revealed a synchronous nystagmoid movement of the face, the palate, and the posterior pharyngeal wall. There was a static tremor of the hands, increased on volitional movement. The tendon reflexes were sluggish and both plantar responses were extensor in type. His speech was "senile," high-pitched, quavering, and badly articulated. He walked only with the help of two assistants. Blood pressure 140/70.

Cases of this kind are of particular importance and deserve detailed clinical and pathological investigation.

Summary

Essential heredofamilial tremor is an interesting affection of not uncommon occurrence. Starting at any age, its progression may be very slow at first, but in the presenium the tremor may spread and become intensified.

The tremor may resemble that of either cerebellar or pallido-striatal disease.

The morbid anatomy of essential heredofamilial tremor is not known.

There is a possible remote relationship with Parkinson's disease and also with the presenile cerebellar atrophies. It is conceivable in some instances at least that essential tremor may represent a forme fruste of one or other of these affections.

An association with palatal nystagmus is very occasionally encountered.

The occurrence of "macrobiotic" traits in the families of essential tremor cannot yet be regarded as proven.

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TRIDIONE THERAPY IN MINOR EPILEPSY

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THE clinical management of epilepsy of the idiopathic type first became possible nearly a hundred years ago when Sir Charles Locock recommended bromides. Phenobarbitone came into use in 1912 when it was advocated by Hauptmann. But neither of these substances was ever satisfactory in the treatment of minor epilepsy. Sodium diphenylhydantoinate (dilantin, epanutin), introduced by Merritt and Putnam in 1938, though it probably remains the most effective drug for control of psychomotor epilepsy, has not proved to be of much value in minor epilepsy.

The anticonvulsant action of tridione (3, 5, 5, trimethyloxalidine—2, 4-dione) was demonstrated experimentally in 1944 by Richards and Everett and first shown to be beneficial in minor epilepsy in 1945 by Perlstein. Since then many American publications have been forthcoming which have shown fairly conclusively that tridione is effective in the control of the various types of minor epilepsy but that it is of no value in major epilepsy and of doubtful value in psychomotor epilepsy. (Davidoff, 1947; Davis and Lennox, 1947; DeJong, 1946; Goodman, Toman and Swinyard, 1946; Lennox, 1945, 1946, 1947; Merritt, 1946; Peterman, 1947; Rickles and Polan, 1947; Thorne, 1945.) Supplies of the drug were not generally available in this country until early in 1947 and so far there have been few published reports here dealing with its effect in minor epilepsy. (Briggs and Emery, 1949; Butter, 1948.)

For the past two years we have investigated the value of the drug in minor epilepsy at a clinic for epileptics. Routine neurological investigation was carried out and patients were instructed in the nature of the study and provided with diary sheets to record their attacks as far as possible and to note any side-effects. They were seen at the clinic at intervals of three weeks and we believe we now have sufficient experience of the drug to record our estimate of its value.

CLASSIFICATION OF THE CASE MATERIAL

We have adopted the classification of epilepsy which clinical and electroencephalographic experience has suggested in recent years. It is

not alleged that such a classification adequately covers all types of seizures —indeed, on clinical grounds alone, and sometimes even with the aid of the electroencephalogram, the clinician will encounter great difficulty in classifying some types of attacks. But on the whole epilepsy may be conveniently grouped into three main categories—major, minor and psychomotor epilepsy. The different types of attacks may be idiopathic or symptomatic of underlying disorder and they usually coexist to some extent. Major epilepsy is certainly the commonest of the three and psychomotor epilepsy the least common.

Minor epilepsy most commonly manifests itself in childhood and adolescence. Unlike major epilepsy, it rarely starts after the age of twenty-five years. The majority of patients with minor epilepsy also experience major attacks, especially after the twentieth year. The form of the minor attack varies considerably. It usually consists of a transient interruption of cerebral function. Nothing positive actually happens in many cases; there is merely a disturbance of consciousness. But this disturbance—momentary though it may be—can recur with such frequency as to handicap the patient considerably. He may "blot out" hundreds of times a day or he may have serial attacks in which awareness and response are absent or grossly reduced and performance of even the simplest actions made impossible.

At this end of the scale, then, fleeting disturbance of consciousness is the sole clinical manifestation of the single attack of minor epilepsy. But if the disturbance of consciousness is severe or longer, the patient may slump in his chair or fall to the ground. He is not convulsed and any increase of muscle tone is usually slight and transient. True, there occasionally appears some twitching of the eyelids or mouth or perhaps of the fingers. A few patients make a gurgling sound or smack their lips but on the whole there is little motor activity. During such a spell the patient may cease what he is doing—a book may fall from his hand, he may stop talking in the middle of a sentence or may mutter incoherently. If the attack is sufficiently disturbing of consciousness that the patient falls to the ground he may injure himself. Tongue-biting is rare as convulsion does not occur but incontinence may be a distressing feature of some attacks.

For the first type of attack, which is most frequent in children and in which simple "ruffling of the surface of consciousness" occurs, the term *pyknolepsy* has been used for many years. But it is merely one variety of simple *petit mal* and there is no peculiar feature which separates it from the other forms.

In the second type there is sudden slumping or falling to the ground with or without any apparent disturbance of consciousness. Recovery is

rapid—"I drop like a stone, but I'm up immediately"—is a typical remark. This is designated an *"akinetic attack."*

A third and rarer form of minor epilepsy is that termed the *myoclonic* attack. Here the essential feature is a sudden involuntary movement of a limb. There is a quick jerk, usually of the flexor muscles of one or both arms, with perhaps a turn of the head or a grimace. It is over in a flash. Such attacks often occur on waking or during the first hour thereafter. They may occur at the breakfast table. One does not often hear a patient complain of such attacks voluntarily; he usually has not recognized them as a feature of his epilepsy and is surprised when informed of their significance. The parent of a child so afflicted usually ascribes them to "clumsiness" as often some mishap occurs at table. They are not "Jacksonian" attacks.

The *"petit mal* triad" consists of these three types of epileptic seizures. They have in common a characteristic disturbance of the electroencephalogram and a tendency to respond satisfactorily to treatment by tridione. They are little affected by other anti-convulsant substances.

A correct clinical diagnosis of minor epilepsy can usually be made without difficulty and without electroencephalography. But in some instances, especially when the clinician has not a clear picture in his mind of what constitutes minor epilepsy, cases may be incorrectly labelled. There has been a tendency to use the term *"petit mal"* whenever such overt phenomena as tongue-biting, convulsion and incontinence are absent. The mother of the child might say "They are not bad fits" or the educated person, disliking the terms "convulsion," "fit," or "epilepsy" may speak of *"petit mal."* We have noticed the misuse of the term *"petit mal"* in doctors' letters which have accompanied patients to our clinic. It is clear that in assessing the value of a drug in the treatment of minor epilepsy one should be quite certain just what is meant by that term. We have observed that tridione may be unjustly discarded because it was found ineffective in controlling attacks which were certainly not minor in character. There are all grades of the *grand mal* convulsion and tridione is certainly ineffective in them all—whether the fit is slight or severe.

Again, when a patient is suffering from many major and minor attacks it is difficult to distinguish some of them. Occasionally minor ones precipitate a convulsion or they may follow after it and the best therapeutic result may be obtained only when the first type of fit is controlled. We have observed this several times. Serial attacks of minor epilepsy are also sometimes described by the patient or parent as "a severe attack." "He was out for hours" or "He was not right all day." The duration of the whole disturbance suggests to the practitioner that this cannot be *"petit mal."* But tridione, in our experience, may be strikingly

beneficial in such cases whereas bromide, phenobarbitone and sodium-diphenylhydantoinate are unsatisfactory.

When we come to the question of psychomotor epilepsy there are several difficulties. Between major and minor epilepsy there is a group of cases in which consciousness is not lost and convulsive phenomena do not occur. They have been variously described as epileptic equivalents, fugues, furor states, automatisms, psychomotor variants or psychomotor epilepsy. They are not easily classified but consist mainly of episodes of bizarre motor activity, sensory hallucinations and illusions, or acute autonomic disturbances. They have to be distinguished on the one hand from psychotic states and emotional behaviour disorders and on the other hand from major and minor epilepsy. Without electroencephalography this differentiation may be difficult or impossible and in some cases the effect of tridione cannot be foretold.

In frank attacks of psychomotor epilepsy the motor activity may be so odd that minor and major epilepsy can be promptly excluded. In other instances, however, only simple automatic action occurs—such as drumming the fingers, clapping the hands or stamping the feet. There is obvious mental confusion and amnesia, varying in degree, following the incident. The patient sometimes believes he remembers what happened but close questioning reveals that there was considerable unawareness at some period of the episode. On the sensory side there may be vague illusions or vivid hallucinations. Objects may appear merely "funny," or "strange," or "small" and sounds distant, distorted or meaningless. It is these short-lived, psychomotor (used in this sense as including psychosensory) attacks, which may be confused with *petit mal*. Although the psychomotor attack is usually of longer duration than the simple *petit mal* episode, serial attacks of *petit mal* may produce a state of confusion and amnesia closely resembling a psychomotor event. *Simple* automatism may occur in either form of attack but it is much commoner in the psychomotor seizure; the more complex forms of automatism seem never to occur during simple *petit mal* but may follow the temporary disturbance of consciousness. Penfield (1946) has pointed out that automaticity may be considered as ictal or post-ictal. The former is commonly referred to as *petit mal*.

The differentiation of *petit mal* and psychomotor epilepsy is important as tridione appears to be effective only in the former. We have studied cases in which tridione has been tried and discarded in disappointment, in which there were clearly no episodes of minor epilepsy—but transient psychomotor attacks. On the other hand there have been cases in which the attacks seemed to have been something more than simple minor epilepsy and yet the electroencephalogram revealed typical "spike and

wave" abnormality and tridione proved effective. A careful history in these cases often reveals additional, though infrequent, seizures typical of one or other of the *petit mal* triad. Occasionally, however, the effect of tridione cannot be foretold, as in Case 2, where clinically the attacks suggested psychomotor disturbance and the electroencephalogram was normal, yet the seizures were completely controlled.

It is evident, therefore, that although the majority of epileptic phenomena can be correctly classified under such titles as "major," "minor" and "psychomotor," there are cases in which clinical judgment alone is not sufficient. The pattern of the electroencephalogram and the response to drugs should also be taken into consideration.

The Case Material.—We have studied the effects of tridione in 50 epileptic individuals since January 1947. In 45 a clinical diagnosis of minor epilepsy was first made and in the remaining 5 tridione was used although we had some doubt about the likelihood of obtaining a satisfactory response.

The relevant data are set out in Tables I and II. There were 19 males and 31 females. 45 had periodic minor seizures. In 5 the attacks were psychomotor. 34 patients also suffered from major epilepsy and/or from psychomotor attacks.

The three types of manifestation of minor epilepsy were distributed as follows:—

(1) Simple *petit mal* (pyknolepsy) ...	36
(2) Akinetic attacks	20
(3) Myoclonic attacks	8

From Table I it will be seen that many patients were experiencing more than one attack of a minor character. In none of our patients was there any evidence of underlying organic disease. They were all considered to be examples of "idiopathic epilepsy."

In Table II are outlined the types of seizure, other than *grand mal* convulsions, which our patients were experiencing, and for which tridione therapy was instituted. We think it important to offer this evidence so that correct comparisons may be made with other published series. We doubt whether all clinicians would agree, on purely clinical grounds, concerning this question of the differentiation of major, minor and psychomotor seizures.

Dosage.—In general we commence treatment with one capsule (0·3 gramme) thrice daily. In the majority of patients this has proved to be the optimum dose. Children do not appear to be less tolerant of tridione than adults. The maximum doses employed were 0·6 gramme thrice daily (in Case 9), a dose which increased the degree of control of the minor epileptic seizures beyond that achieved by the usual optimum.

Patients who showed the most satisfactory response to tridione in no case required more than 0·3 gramme four times daily. Indeed, in many of our patients we have been able to reduce doses considerably after satisfactory control had first been established on larger amounts. We are studying the clinical and electroencephalographic effects of the gradual withdrawal of tridione in cases where satisfactory control was achieved with average dosage. Recurrence of minor epilepsy is usually delayed for some days or weeks if the drug is discontinued. In some cases effective control may be procured with very small amounts of tridione (e.g. 0·1 gramme daily). This is of obvious importance in view of the potentially toxic properties of the drug.

Where severe toxic reactions were observed (Cases No. 6, 27, and 45), necessitating discontinuation of tridione, control was later attained with much smaller doses (0·3 gramme daily, 0·1 gramme daily and 0·3 gramme daily, respectively), without mishap.

Results of treatment.—Tridione produced a satisfactory response in the control of minor epileptic seizures in 38 out of 45 cases.. By "satisfactory" we mean that a significant reduction in the incidence of attacks, or their complete control, was achieved (*see* Table I). 5 of the 7 remaining patients (Cases 13, 20, 34, 44 and 49) were improved by tridione but they were still experiencing daily or almost daily attacks. In two patients (Cases 23 and 25) tridione was ineffective.

The frequency of simple *petit mal* before and after treatment is, of course, difficult to assess accurately in some patients—children for example; but the state of affairs revealed by careful enquiry is represented in the figures we quote. They give a reasonable indication of progress.

We adduced no evidence that tridione was more effective in any one particular type of manifestation of minor epilepsy. It seems to be equally effective in the three types of minor seizure—simple *petit mal*, the akinetic episode and the myoclonic attack. We have observed that an occasional akinetic episode may occur in cases of simple *petit mal* successfully controlled by tridione in which no previous akinetic attacks had occurred (Cases 17, 36 and 41).

In the 2 failures (Cases 23 and 25), both patients were severely afflicted with major epileptic convulsions. Case 23 had as many as five and Case 25 as many as three convulsions daily. In Case 23 we subsequently gained the impression (without electroencephalography) that the majority of the attacks, although short-lived, were not minor epilepsy. In Case 25 there appeared to be typical but infrequent episodes of the kind which, in our experience, respond to tridione. Many attacks in this case were probably abortive *grand mal* with post-ictal automatism.

In 5 patients (Cases 32, 38, 39, 40 and 50), a clinical diagnosis of psycho-

motor epilepsy was made but as treatment with other drugs had proved unsatisfactory, the effect of tridione was tested. All five patients were made distinctly worse by this treatment—the attacks were more frequent and more severe.

We noticed no constant effect of tridione on *grand mal* seizures. When they are also present other anti-convulsants, in addition to tridione, are necessary.

Side-Effects of Tridione Therapy

There are three main side-effects—photophobia, skin eruptions and disturbance of blood cell formation. A few patients may complain of nausea, depression or fatigue but they are transient and not serious symptoms.

Photophobia was experienced by 11 (22 per cent). It was described as a sensitivity to bright light but in the majority it cleared up spontaneously after a few weeks, without discontinuing medication. We have used the term "photophobia" to embrace a number of subjective visual phenomena. Some patients describe a true intolerance of bright light, but many state that objects simply appear white—as if covered in snow. Yet others experience a blurring of vision which in most cases is transitory, passing off as vision becomes adapted. One patient described diplopia.

Sloan and Gilger (1947) have carefully studied the visual effects of the drug and found evidence of temporary impairment in acuity, brightness sensitivity, colour discrimination and sensitivity to flicker when the field of vision was illuminated at high brightness. They concluded that the drug produced its visual effects at the retinal level, probably on the neural layers rather than on the photochemical process. Experimental investigation has revealed no indication of injury to the optic nerves, but Lennox (1945) refers to three cases of "toxic amblyopia," due to the drug, which he has heard of in the United States.

The appearance of a few macules or papules on the face, forehead or trunk is not uncommon during treatment. Three of our patients, however, developed a severe skin reaction which necessitated stopping treatment. In the first (Case 6) an urticarial eruption appeared on the fourteenth day of treatment. It developed over face and trunk and was followed by erythema and desquamation. It cleared up after two weeks but recurred one month later when tridione was recommenced in small doses. Six months later tridione was used in full dosage with beneficial effect and without mishap. During the eruptive stage the white cells showed no significant reduction in numbers.

In the second (Case 27) the rash appeared on the seventeenth day of treatment. General pruritis, œdema and cyanosis of the face, conjunctival

injection and swelling and widespread exfoliation subsequently developed. The blood-count remained normal and the condition cleared up without further complication in three weeks. Two months later tridione was cautiously recommenced, beginning with one capsule (0·3 gramme) a week, and effective control of *petit mal* and myoclonic seizures was ultimately obtained without further mishap.

A third case in whom attacks had been abolished with 0·3 gramme of tridione thrice daily (Case 45) developed acute erythema and œdema of the face on the thirty-fourth day of treatment. The drug was withheld and the toxic effect subsided in two or three days. There was no change in the white cell count. Subsequently, treatment was recommenced with one capsule (0·3 gramme) of tridione daily and complete control was achieved. At a later date it was found that a daily dose of 0·1 gramme of tridione was sufficient.

Unfortunately, tridione sometimes exerts a depressant action on red, white and platelet cell formation in the marrow. Anæmia, agranulocytosis and aplasia of the bone-marrow have been reported and in several instances there has been a fatal outcome. Three-weekly white cell counts in our series (Table III) have revealed no serious reduction so far. In the fatal case of agranulocytosis reported in this country by Braithwaite (1948), tridione was continued for twenty-eight days after a rash, lasting two days, had appeared over the thighs. It was continued for a further two days after the development of fever and gingivitis on the fifty-first day of treatment. The patient died seventy-four days after treatment began.

In 4 of our patients (Cases 4, 9, 13 and 44), there was some degree of eosinophilia (30 per cent, 14 per cent, 16 per cent and 7 per cent respectively). In 2 (Cases 19 and 43) there was a transient absolute and relative monocytosis (14 per cent and 11 per cent respectively). 6 patients developed a mild sore throat of transient duration. In these no further toxic symptoms developed and treatment was not interrupted. Gingivitis, adenopathy or splenic enlargement were not encountered.

Davis and Lennox (1947) examined at intervals the blood of 127 patients taking tridione. No decline in platelet counts or hæmoglobin values was observed. The only significant findings were a tendency to neutropenia, eosinophilia and a slight increase in lymphocytes. Neutropenia developed gradually. They advised that patients with a neutrophil count of less than 2,500 should be watched more frequently than once a month, and the use of the drug should be stopped if this count goes below 1,600.

Briggs and Emery (1949), in this country, concluded from a study of the effects of tridione in ten children suffering from *petit mal* that "the toxic complications of tridione proved more dangerous than the disease it

is used to treat." 7 patients were improved but 2 displayed serious toxic effects. Lennox (1949) criticized their conclusion and, with some justification, pointed out that tridione, with its known toxic properties, should be administered with more care than Briggs and Emery had exercised. In Case 9 of their series, tridione was used for two months after the neutrophil count had fallen "below 2,000 per c.mm."—"because of the child's good general condition." The neutrophil count fell to 700 per c.mm. Not until five weeks later, when the neutrophil had fallen to 100 per c.mm., and there was severe depression of all elements of the bone-marrow, was actual treatment instituted. A single transfusion of a quart of fresh blood was then given and the child recovered.

In Case 10 of Briggs and Emery's series, the child developed nephrosis and died. They thought that there was little doubt that a relationship existed between treatment with tridione and the development of the fatal illness. Yet tridione was administered daily during the last five months of life.

The toxic properties of the drug constitute a serious drawback and any physician who employs it must do so with vigilance. But its efficacy is undeniable and we do not feel that it should be generally withheld in the treatment of a condition which may be distressing or even incapacitating. In a well-organized clinic for epileptics it should be possible to prescribe it with a reasonable degree of safety.

Summary and Conclusions

Tridione has been satisfactory in the treatment of minor epilepsy in 38 out of a series of 45 cases. In 12 the attacks were abolished and in another 15 almost complete control was achieved. In 13 further cases there was a significant reduction in the incidence of attacks.

Of the remaining five cases three showed slight improvement. Two failed to respond.

Five patients with psychomotor epilepsy were made worse by tridione.

Minor side-effects—photophobia, mild sore-throat, a few papules on the face, chest or arms—were not uncommon. In two patients there was an urticarial reaction which subsequently developed into generalized exfoliative dermatitis necessitating discontinuation of tridione. In a third case treatment was temporarily discontinued following the appearance of facial erythema and œdema. At a later date tridione was successfully used in these three cases without harmful effects.

Apart from transient eosinophilia in four patients we observed no significant alteration in the leucocyte counts.

We conclude that tridione is the most effective substance as yet avail-

able for the treatment of minor epilepsy. Although serious toxic reactions sometimes occur, they are not common and in hospital out-patient practice tridione is the drug of choice in the treatment of minor epilepsy.

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CEREBRAL LESIONS DUE TO INTRACRANIAL ANEURYSMS[1]

BY

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INTRODUCTION

Frequency of rupture into the cerebral hemispheres.—Cerebral damage is one of the outstanding features of the rupture of intracranial aneurysms, yet the usual conception of rupture is that of an effusion of blood into the subarachnoid space. Indeed, the terms rupture of intracranial aneurysm and subarachnoid hæmorrhage are used almost synonymously. In the relevant literature, with but few exceptions, intracerebral rupture is but briefly mentioned as an infrequent occurrence, or is not mentioned at all. Aneurysms may also produce localized damage by provoking ischæmia. The matter is of more than theoretical interest, for the position and extent of the cerebral damage plays an important part in determining the symptomatology of rupture, the duration of the illness, the prospect of death, and, if the patient survive, the degree of residual incapacity. Finally, an understanding of the pathology is essential in planning the surgical attack upon this pressing problem.

[1]Paper presented at meeting of Royal Australasian College of Physicians in Sydney in October 1947.

Historical Survey

Brinton (1851) found records of 40 cases of intracranial aneurysm in the literature, and he summarized the salient points as follows:

Age: On an average, 42.

Sex: Male to female as two to one.

Site: Anterior or carotid to posterior or vertebral system of vessels, equal; the basilar, one-third of the whole number.

Size: Half "filbert," one-fourth "pea," one-fourth "walnut."

Termination: In one-third only, rupture, or more exactly, in three-eighths rupture; in one-eighth, pressure, simple loss of functions; in one-eighth, congestion or hæmorrhage of brain; in one-eighth, inflammatory conditions of the brain; in one-eighth, coincident disorders or accidents. In three instances the aneurysms were more than one in number; in one instance three were found.

The high percentage of aneurysms upon the basilar artery in Brinton's series and in other compilations (e.g. McDonald and Corb, 1943) is at variance with present experience. It would hardly be expected that the site of congenital and arteriosclerotic aneurysms would alter with the passage of years, hence it seems reasonable to suggest that the involvement of the basilar artery was due to the relative frequency of syphilitic aneurysms in the earlier days. Could aneurysms upon the basilar artery be excluded, it is probable that Brinton's one-eighth with hæmorrhage of the brain would be increased. It is, perhaps, worthy of remark that different authors present very different pictures of the frequency of aneurysms of different arteries, depending upon their clinical experience and the relatively small numbers of cases reported. In cases seen in private practice by the writer there is a much larger percentage of aneurysms upon the carotid artery, although there are few in the post-mortem records herein reported.

Richardson and Hyland (1941) point out that Froin, in 1904, subdivided cases of intracranial hæmorrhage (exclusive of trauma) into three groups: (1) Cerebro-meningeal hæmorrhage—primary intracerebral hæmorrhage rupturing into the subarachnoid space; (2) primary subarachnoid hæmorrhage and (3) meningo-cerebral hæmorrhage—primary subarachnoid hæmorrhage with bruising and erosion of adjacent cerebral tissues. Apparently he made no reference to large intracerebral hæmorrhages, which, in accord with a common tendency, he probably regarded as instances of cerebro-meningeal hæmorrhage.

Collier (1931) mentions that when the hæmorrhage from an aneurysm is slow and when the aneurysm is buried in the brain substance, or has become adherent to and bursts into the brain, the resulting picture is in no

way distinguishable from that produced by cerebral hæmorrhage from other causes.

Richardson and Hyland (1941) alone have appreciated the importance of intracerebral rupture. They studied 118 cases of spontaneous subarachnoid hæmorrhage seen in the Toronto General Hospital between the years 1927 and 1938 inclusively. Of these, there were 57 survivors and 61 fatalities. 27 of the latter group were examined pathologically. In this group, subarachnoid hæmorrhage of varying degree occurred in all, but hæmorrhage was confined to the subarachnoid space in only 8 cases. Thus, intracerebral hæmorrhage occurred in 19 cases. Hæmorrhage occurred into the frontal lobe in 10 cases (arising from aneurysms of the anterior communicating artery in 7 cases, of the middle cerebral arteries in 2, and of the carotid bifurcation in 1). Hæmorrhage occurred into the temporal lobe in 9 (arising from aneurysms of the middle cerebral artery in 5 cases, and of the carotid bifurcation in 4).

In spite of this carefully presented evidence, recent papers show a failure to appreciate the significance of cerebral damage. Magee, in 1943, reviews 150 cases of spontaneous subarachnoid hæmorrhage, with a mortality rate of 56 per cent. Autopsy was carried out in 58 cases, ruptured aneurysms being found in 43. No mention is made of intracerebral rupture. Wolf, Goodell and Wolff (1945), point out that "29 per cent of patients who entered the New York Hospital die during the first episode of bleeding; 14 per cent die during recurrent bleeding between the second and the fourth week after the initial hæmorrhage and an additional 5 per cent die by the end of the first year. The majority of the remaining patients who survive the first year are alive three or four years after the initial hæmorrhage." They recommend that patients who come under observation during the four weeks after a subarachnoid hæmorrhage be subjected to arteriography and subsequent craniotomy if an aneurysm is visualized. However, no mention is made, nor consideration taken, of intracerebral hæmorrhage, which contributes to death in a large number of patients and may reasonably necessitate modifications of the surgical attack.

Dandy (1944) in his classical monograph upon the surgical treatment of intracranial aneurysms notes the occurrence of hemiplegia, and believes that this strongly suggests hæmorrhage from an aneurysm upon the middle cerebral artery. Monoplegia he believes to be fair evidence that the lesion is on the anterior cerebral artery, and bilateral motor loss of an aneurysm of the basilar or vertebral arteries. He believes that rupture into the subarachnoid space usually causes death, but if bleeding occurs into the brain, the adjacent tissues may stop the hæmorrhage and prevent immediate mortality. It will be seen that these postulates are incorrect.

Case Reports

The first 10 cases were seen consecutively at the Royal Melbourne Hospital during the last six months. All presented evidence of cerebral damage.

Case 1.—Aneurysm of the middle cerebral artery. Rupture into frontal lobe. Mild contralateral hemiplegia with rotation of head towards the weak side. Terminal tonic fits.

A male, aged 23, was found lying unconscious in the lavatory of a railway carriage. He had vomited and passed urine into his clothes. As a strong odour of alcohol was noticed he was placed in the hands of the police at the rail-terminus. However, as no improvement had occurred by the next morning he was brought to hospital. Subsequently, his sister stated that he had complained of severe headaches during the last five years and had been very irritable.

It was possible to rouse the patient after admission to hospital, but after a brief display of irritability he quickly lapsed into stupor. His head was turned towards the left side, and occasionally the right corner of the mouth twitched. He was able to move all four limbs. The deep reflexes were very brisk, especially on the left side; the abdominal reflexes were absent and the plantar responses extensor. There was marked cervical rigidity and Kernig's sign was present on each side. The cerebrospinal fluid was evenly and heavily blood-stained, its initial pressure being 90 mm.

Subsequently he improved, although he remained confused and disorientated. He believed that he had fallen from the train on to a platform, striking the right side of his head. During the next few days he continued to complain of headache, although it became less severe. The right pupil was larger than the left, and the left-sided limbs were weak. Both plantar responses remained abnormal. Subsequently the weakness became less marked and he was almost free from symptoms. Arteriography was planned, but sixteen days after the onset he again complained of severe headache in the right temporal region. Within a few minutes he lost consciousness. His head was turned to the left and arched backwards, the right upper limb was strongly flexed at the elbow and the left was extended, except for flexion at the wrist. The lower limbs were extended. He remained in this state for some minutes, and when he recovered consciousness there was no detectable difference between the strength of the limbs on the two sides of the body, although the power was generally reduced. The deep reflexes were more active than before and clonus could be elicited on each side. He complained of very severe headache and vomited. Three similar fits ensued and he died suddenly with respiratory failure and intense cyanosis three-and-a-half hours after the onset of the first fit.

There was a thick mass of blood clot over the anterior surfaces of the pons and medulla, in the cerebello-pontine angles and in the cisterna magna (fig. 1A). Its appearance suggested that blood had escaped from the 4th ventricle. Otherwise, very little blood was to be seen in the subarachnoid space over the brain. The arteries of the circle of Willis appeared normal. At first sign no abnormality of the basal vessels was obvious and there was no blood between the frontal lobes or in the sylvian fissures. However, within the right sylvian fissure the middle cerebral artery appeared to divide into three trunks of equal size. Two of these continued normally along the sylvian fissure, but the third appeard to pass into the frontal lobe at the lateral extremity of the anterior perforated substance (fig. 1B). Normally, only small vessels penetrate the brain substance in this situation. Dissection showed it to be the elongated neck of an aneurysm which was embedded in cerebral substance. Section of the brain showed an aneurysmal sac, 8 mm. in diameter, containing, and embedded in, blood clot. The blood had extended forwards and upwards below the head of the caudate nucleus (fig. 1c). Further laterally the

clot was more extensive and there was destruction of white matter and infiltration with blood as far posteriorly as the middle of the body of the ventricle. The blood had ruptured into the floor of the anterior horn of the left lateral ventricle. The lateral, 3rd and 4th ventricles were filled with blood clot.

It is of interest to note that such an aneurysm as this might be overlooked, and, if the patient were older, a diagnosis of primary intracerebral hæmorrhage made. The stem of the aneurysm could be readily mistaken

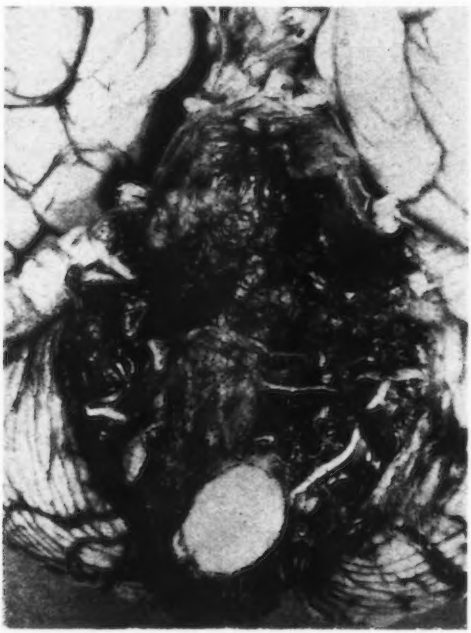

FIG. 1A.

FIG. 1B.

FIG. 1c.

FIG. 1 (*Case* 1).—(A) Blood clot in the cisterna magna and over the ventral surface of brain-stem. Note absence of blood elsewhere in subarachnoid space. (B) Neck of the aneurysm in the sylvian fissure, at the first major bifurcation of the middle cerebral artery. (C) Distribution of blood through the posterior inferior part of the frontal lobe, into the frontal horn of the lateral ventricle and thence through the ventricles into the cisterna magna, medullary and pontine cisterns.

for a branch of the middle cerebral artery, and the wall of the aneurysm, embedded as it was in blood clot, could escape notice, especially if the brain were examined immediately after removal. There was no subarachnoid hæmorrhage in the usual sense, for the blood gained the subarachnoid space only after passing through the ventricles. In another similar case, blood first appeared in the cerebrospinal fluid five days after the initial catastrophic onset.

Case 2.—Aneurysm of the bifurcation of each internal carotid artery. Rupture into one frontal lobe. Aphasia; flaccid hemiplegia.

A man, aged 47, was found slumped over his office desk. He appeared to be confused and was unable to speak clearly. His wife stated that he had complained of occipital headache and tiredness for a period of three weeks. He had been refused life insurance after his renal function had been investigated.

There was aphasia (of motor type), weakness of the right lower facial muscles, and of the right side of the tongue. The power and tone of the limbs appeared equal on each side, the tendon reflexes were equal and active, the abdominal reflexes were absent on the right side and the right plantar response was extensor. The blood pressure was 120/100.

At the end of five days he had recovered sufficiently to describe the terrific headache and coincident stiffness of the neck which preceded the initial loss of consciousness. He complained that his memory was poor and that he still had some difficulty in speaking. On the next day the cerebrospinal fluid was found to be straw-coloured, and under an initial pressure of 230 mm. On the following day he suddenly lost consciousness. There was gross opisthotonus, with extreme extensor rigidity of the right upper and lower limbs and less marked rigidity of the left limbs. The pupils were dilated and breathing was stertorous. The right arm then began to twitch. He recovered consciousness, sweating profusely, at the end of ten minutes. A second similar attack was preceded by pain in the forehead. After the attacks the physical signs were as described above, except for an increase of cervical rigidity and slowness of the pulse.

Five days later another similar attack occurred, but consciousness did not return and respiration remained stertorous. The right limbs fell to the bed more rapidly than the left, and, in contrast to the left arm and leg, did not move in response to painful stimulation. The muscles on the right side were more flaccid than those on the left, the tendon, abdominal and plantar responses were absent. He died several hours after the last attack.

The subarachnoid space was filled with blood throughout. There was some depression of the cerebellar tonsils. Dissection of the circle of Willis revealed the presence of two aneurysms, each growing at the point of bifurcation of the internal

FIG. 2 (*Case* 2).—Symmetrically placed aneurysms at the obtuse angle between the anterior and middle cerebral arteries. The aneurysm on the left is embedded in blood clot within a thin shell of frontal lobe tissue.

carotid artery, from the obtuse angle between the anterior cerebral and middle cerebral arteries (fig. 2). The aneurysm on the right side, 3mm. in diameter, was unruptured. That on the left side appeared to be adherent to the posterior part of the inferior surface of the frontal lobe just lateral to the posterior extremity of the olfactory tract and under cover of the tip of the temporal lobe. On section of the brain, the sac, 4 mm. in diameter, was seen to be embedded in blood clot in the inferior part of the frontal lobe. The fundus of the aneurysm contained blood clot and rupture had occurred in the anterior part of the wall. The blood had ploughed up a considerable portion of the lower part of the frontal lobe in this region. Posteriorly it reached as far as the interventricular foramen, remaining lateral to the putamen.

Case 3.—Aneurysm of the anterior communicating artery. Rupture into both frontal lobes. Convulsions with tonic and clonic phases. In between attacks muscles weak and flaccid with extensor plantar responses.

An Italian male, aged 41, was admitted to hospital within twelve hours of the onset of his illness, in an irritable and resistive state. Neither he nor his friends had much English, but it was gathered that he had awakened during the preceding night with abdominal pain and vomiting. Subsequently he complained bitterly of his head.

The only abnormal signs were those indicating meningeal irritation; cervical rigidity and Kernig's sign on both sides. The blood pressure was 200/115. Evenly blood-stained fluid, under greatly increased pressure, was evacuated by lumber puncture.

The history and findings suggested the diagnosis of subarachnoid hæmorrhage from a ruptured intracranial aneurysm. It seemed probable that the initial symptoms of abdominal pain and vomiting were not symptoms of the rupture but rather were associated with his insanitary method of feeding. The increase of venous pressure occasioned by the vomiting may, however, have provoked the rupture.

The clinical state improved until, on the ninth day, a series of three fits occurred. When seen after the first fit he was lying unconscious. Suddenly his body stiffened, with extended head and rigid flexed arms. His lower limbs were

FIG. 3A.

rigidly extended, respiration ceased and he became cyanosed. The tonic contraction then broke into clonic convulsive movements, which became coarser and more irregular before finally the muscles relaxed.

In the third fit the head and eyes became strongly deviated to the right. The right arm moved restlessly, both arms became raised from the bed, the elbows being flexed. Some wild, jerky movements now occurred in both arms and head. Then the upraised right arm became rigidly immobile and the left arm travelled across in a semi-voluntary fashion to support it. Then coarse and rhythmical twitching supervened in the right arm. Both lower limbs exhibited clonic contractions, the movements being coarser on the right side and at this stage the left upper limb also twitched.

The two different types of fit suggested that both motor cortices were being

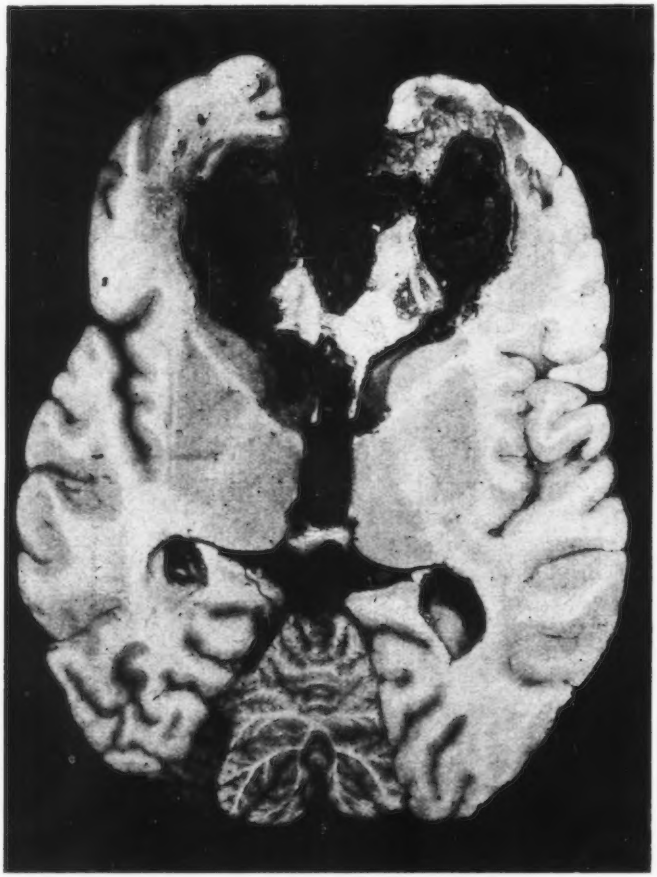

FIG. 3B.

FIG. 3 (*Case* 3).—(A) Small ruptured aneurysm growing from the junction of the left anterior cerebral and anterior communicating arteries. (B) Laceration of frontal lobes.

stimulated, in one attack the left side more than the right. It was thought that further hæmorrhage was now occurring from the aneurysm, and affecting both cerebral hemispheres. Bilateral involvement suggested that the aneurysm was situated upon the anterior cerebral or the anterior communicating arteries.

The cerebrospinal fluid did not contain fresh blood on the next day, but was brightly yellow in colour, presumably from the previous subarachnoid effusion. He remained in a comatose state for two days. During this time, the muscles were flaccid. The deep and abdominal reflexes were absent and the plantar responses were extensor. However, on the third day it was possible to rouse him and he was able to move all limbs. Suddenly, however, he lost consciousness, respiration ceasing momentarily before becoming stertorous. The cerebrospinal fluid was now heavily blood-stained. After this the patient remained comatose and incontinent with flaccid limbs and extensor plantar responses, until he finally died of medullary failure on the seventeenth day of his illness.

At autopsy the subarachnoid space contained much blood. A small aneurysm, 2 by 3 mm. in size, was found growing from the junction of the left anterior cerebral artery and the anterior communicating artery (fig. 3A). Blood clot surrounded the sac and extended into the great longitudinal fissure between the frontal lobes. The medial surface of the frontal lobes was lacerated. Horizontal sections of the brain showed that blood clot extended anterior to the caudate nuclei, ruptured into the anterior horns of each lateral ventricle and extended farther forwards in the medial part of the central white substance of the frontal lobes almost to the frontal poles (fig. 3B).

In another patient (Case 4) an aneurysm of the anterior communicating artery had ruptured into the posterior inferior parts of the frontal lobes. There were no fits and, although obviously ill, the patient was able to move all limbs, although muscular power appeared to be slightly reduced. The muscles were flaccid, the tendon reflexes were absent, the abdominal reflexes were absent and the plantar responses were extensor.

Case 5.—Aneurysm of the anterior cerebral artery. Rupture into both frontal lobes. Localized convulsions followed by monoparesis, later attacks suggesting decerebrate rigidity. Subsequently arms flaccid, lower limbs extended.

A male, aged 28, was admitted to hospital in a state of coma. His wife stated that he had been nervy for some years, and on several occasions had expressed a desire to leave the city and live in the country. He had complained of occasional headaches during the last ten years. Eleven days before admission he awakened at 3 a.m. with severe frontal headache, spreading intermittently over the vertex to the suboccipital region, when the sinews at the back of his neck would go into spasm, pulling the head backwards. The severe pain abated after three hours, leaving a feeling of dullness and heaviness of his head. However, he continued to work, complaining of general lassitude and some headache. At 9 p.m. on the evening before admission, he complained of very severe frontal headache, and walked about the room holding his head. His wife could get no sense out of him and thought that he was going out of his mind. He was still stumbling about the room as she dropped off to sleep. She was awakened at 6.30 a.m. by an unusual noise, and on investigating it she found her husband lying unconscious outside the bedroom door.

On admission to hospital two hours later he responded to painful stimulation with movements of the left hand, but not of the right. The pupils were very

small and did not react to light. The right lower facial muscles were weak. The tendon reflexes were absent on the right side and reduced on the left. The abdominal reflexes were absent and the plantar responses equivocal. Following lumbar puncture (which evacuated blood-stained cerebrospinal fluid under an initial pressure of 240 mm.) he roused and complained of pain in the left side of the face which he rubbed vigorously. There was definite weakness of the right limbs. Then followed three convulsive attacks involving the right upper limb and associated with loss of consciousness. Each attack lasted some thirty seconds. He remained comatose for thirty minutes and on recovering consciousness the power, although reduced, was found to be equal on both sides. The right facial paralysis was no longer evident. The pupils were widely dilated and the ocular axes were imparallel.

Ten minutes later he began to suffer from a series of twelve attacks, each lasting from five to ninety seconds. In between the initial attacks he regained consciousness, and in this state the limbs were flaccid and paralysed. The elbows were slightly flexed, the lower limbs extended. The deep reflexes were absent and plantar stimulation evoked no response. Suddenly the limbs would pass into rigid spasm. The upper extremities were adducted at the shoulders, with extended elbows, pronated forearms, and flexed or dorsiflexed wrists. The fingers were curled into the palms, with the thumbs in close apposition. The lower limbs were rigidly extended, and the feet were plantar flexed. The spasm in the arms varied with respiration. During inspiration the elbows passed into a slightly flexed posture and were pliable. With each expiration the elbows became forcefully extended. The lower limbs remained rigidly extended throughout. At the termination of each attack the respiration became quieter, the upper limbs flaccid, although the lower limbs remained rigid. The pulse rate, at first slow, increased to 152, the systolic blood pressure rose to 210 mm. mercury, and the temperature was 101·2° F. He failed to recover consciousness after the first few attacks and death occurred two hours after the onset of the spasms.

The subarachnoid space throughout contained bright blood. The pontine and medullary cisterns, the interpeduncular cistern and the cerebello-pontine angles were occupied by thick clot, which emerged from the foramen of Magendie (fig. 4A).

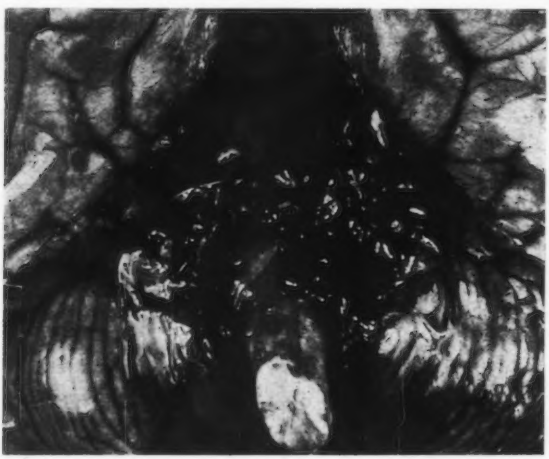

FIG. 4A.

The arteries of the circle of Willis were thin-walled. On separating the inferior portions of the frontal lobes, anterior to the anterior communicating artery, an elongated aneurysmal sac (1·2 cm. in length and 0·5 cm. in width) was seen lying between the two anterior cerebral arteries. It opened anteriorly into the left anterior cerebral artery at its initial bifurcation (fig. 4B). The aneurysm had ruptured, and blood had passed into the substance of each frontal lobe, rupturing into the floor of each frontal horn. The area of destruction was situated in front of the head of the caudate nucleus on each side, and extended above the apertures in the frontal horns, skirting around the tips of the ventricles and the genu of the corpus callosum to within 1 cm. of the frontal poles. On the right side the hæmorrhage was fresh, occupying a ragged cavity in the frontal lobe. On the left side there was a smaller slit-like cavity with brown-stained walls, evidently of more remote origin than that on the right side (fig. 4B).

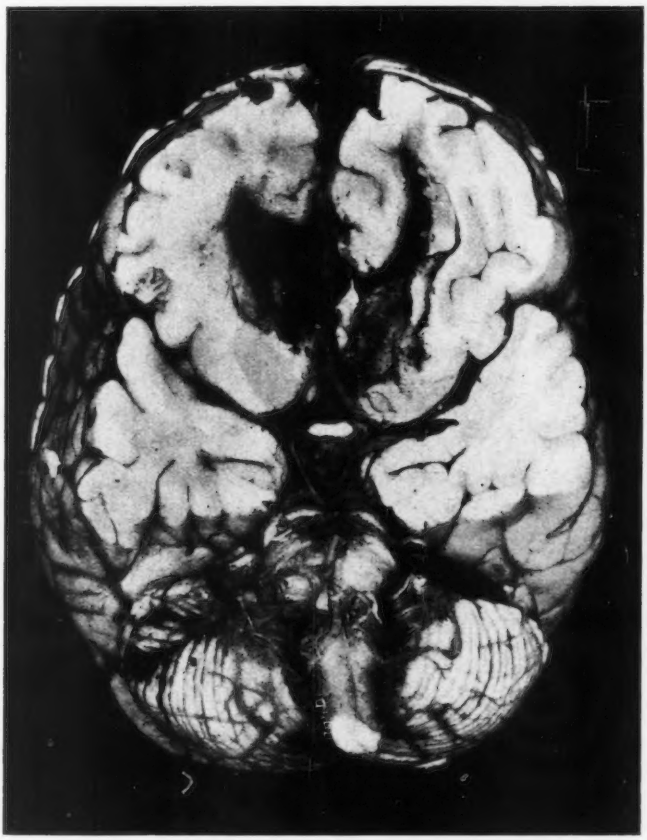

FIG. 4B.

FIG. 4 (*Case* 5).—(A) Blood clot over brain-stem. (B) Aneurysm of anterior cerebral artery rupturing into each frontal lobe (clot has been removed from brain-stem).

Case 6.—Aneurysm of middle cerebral artery. Rupture into one frontal lobe. Flaccid hemiplegia. Evacuation of blood clot with recovery of power.

A male, aged 49, collapsed under the shower two days before admission to hospital. On recovering consciousness he was paralysed on the left side and complained of severe frontal headache. Thirty-six hours after the onset he lost the ability to speak. During examination he appeared confused and prone to fall asleep. His speech was slurred and unintelligible. The upper limbs were held rigidly, the right moving more than the left. The left lower limb was flaccid and weak. The tendon reflexes were less active on the left side than on the right, the abdominal reflexes were absent, the right plantar response was flexor and the left extensor. No sensory loss was detected. The blood pressure was 150/100. The cerebrospinal fluid was under an initial pressure of 260 mm. and was evenly blood-stained. The very severe headache gradually subsided and speech became clearer, but the hemiplegia remained.

The step-like development of the symptoms, the evidence of early subarachnoid hæmorrhage and the absence of evidence of arteriosclerosis was thought to favour the diagnosis of intracerebral rupture of an aneurysm. Nine days after the onset Mr. R. S. Hooper carried out angiography. The anterior and middle cerebral vessels were well outlined, but no aneurysmal sac was apparent. Just above the sylvian point the branches of the middle cerebral artery appeared to be unusually straight. In the antero-posterior film the first portion of the anterior cerebral artery was displaced to the left. These two deformities suggested the presence of a space-occupying lesion in the posterior portion of the right frontal lobe. Eight days later Mr. Hooper aspirated old blood and disintegrated brain tissue by means of a needle introduced through a right frontal burr hole. Within a few days the strength of his left side had increased and he was able to walk ten days after the operation.

Although the diagnosis of aneurysm has not been proven, it is considered to be probable. The failure to visualize a sac by arteriography is not evidence of the absence of an aneurysm. The evacuation of blood clot was followed by remarkably rapid recovery, perhaps to a greater extent than would follow an intracerebral hæmorrhage, which is usually attended by more destruction because of the ischæmia induced in the territory of the affected vessel. The rapid recovery suggested that the hemiplegia was due to compression, rather than to destruction, of the pyramidal fibres. In any case, it is not unreasonable to assume that Mr. Hooper's successful method of treatment in this case may be added to the surgical procedures of value in the treatment of aneurysms. When the frequency of intracerebral rupture is considered, this point becomes all the more important. Obliteration of the aneurysm alone would not have resulted in such complete resolution of the hemiplegia. It is possible that in a number of cases clotting and organization lead to spontaneous sealing of the aneurysmal sac.

Case 7.—Aneurysm at junction of anterior and middle cerebral arteries. Rupture into frontal lobe. Extensor rigidity of all limbs, with extensor plantar responses.

A woman, aged 32, was found unconscious half an hour before admission to hospital. The left side of her forehead was bruised and lacerated, and there were abrasions on the volar surfaces of the wrists. The pulse rate was 52, the respiratory rate 40, and the blood pressure 220/110. The urine contained albumen. The pupils were dilated and did not react to light. The arms were adducted and internally rotated and the elbows were extended. There was marked rigidity of the extensor muscles of the lower limbs. The deep reflexes were equally active, the abdominal reflexes were absent and the plantar responses extensor. There was cervical stiffness and bilateral Kernig's sign. The cerebrospinal fluid was heavily blood-stained, its pressure being low. The patient died soon after admission.

The anterior surface of the pons and medulla was covered with a thick layer of blood clot which extended into the interpeduncular fossa and into the cerebello-pontine angles, spreading thence some distance over the anterior surface of the

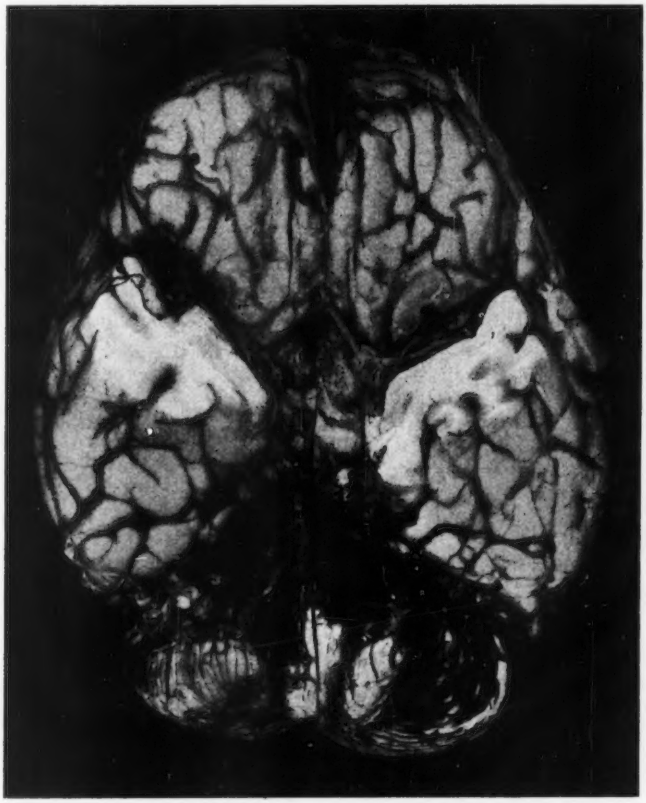

FIG. 5 (*Case* 7).—Protrusion of brain tissue anterior to the optic chiasma caused by intracerebral rupture. The neck of the aneurysm can be seen in the obtuse angle between anterior and middle cerebral arteries on the left side. There is little general subarachnoid hæmorrhage, but a large clot is seen in the pontine cistern.

cerebellum (fig. 5). The cisterna magna was full of blood clot and the appearances suggested that the blood had emerged from the foramen of Magendie and passed along the lateral surfaces of the medulla to form the large clot already described. The optic chiasma was displaced backwards, to the right and downwards by a mass which presented chiefly to the left side of the mid-line between the left optic tract, the termination of the left carotid artery and the left anterior cerebral artery, extending almost as far forward as the anterior communicating artery. The surface of the mass was white and coarsely granular. The left posterior communicating artery ran across the mass which had been thought to be a neoplasm. On opening up the medial part of the left sylvian fissure an aneurysmal sac was seen to be growing from the obtuse angle of junction of the anterior and middle cerebral arteries (fig. 5). Its fundus was adherent to the posterior part of the inferior surface of the frontal lobe in this region, lateral to the excrescence already described. Median section of the brain showed the 3rd, lateral and 4th ventricles to be filled with blood clot, and there was a large mass of blood clot in the lower posterior part of the left frontal lobe, continuous with that in the lateral ventricle. A mass of brain tissue composed chiefly of the caudate nucleus was displaced downwards to rupture through the medial surface of the hemisphere and present between the frontal lobes anterior to the lamina terminalis and optic chiasma. It extended across the median line, forming a depression, anterior to the optic chiasma, in the median surface of the right frontal lobe. The anterior part of the fornix and the posterior part of the rostrum of the corpus callosum appeared to have been ruptured. The interventricular foramen was displaced backwards, shortening the 3rd ventricle into a cavity about 1·8 cm. in antero-posterior extent.

The features of interest are the disruption of the brain which led to the appearance of a tumour-like excrescence which displaced the anterior part of the 3rd ventricle and the optic chiasma. An aneurysm growing at the termination of the internal carotid artery, and rupturing into one frontal lobe, produced bilateral extensor rigidity. It will be noted that the type of rigidity was somewhat similar in three cases in which a thick layer of blood clot presented on the ventral surface of the brain-stem. The phasic variation seen in one case is a very unusual phenomenon. It seems reasonable to assume that this type of rigidity, suggesting the decerebrate type, is caused by the accumulation of blood clot over the brain-stem. Direct irritation of pyramidal fibres or shift of the brain-stem seems to be an unlikely cause, although the complaint of facial pain by one patient was probably due to irritation or displacement of the corresponding trigeminal nerve. It is unlikely that blood escaping from another artery could compress the basilar artery or its branches. Nor is it likely that contraction of blood clot could compress the artery, if only because death occurred soon after the initial bleeding in one case. It is conceivable that capillaries in the brain-stem might be compressed between blood in the 4th ventricle and in the pontine and medullary cisterns. On the whole, it seems most likely that the clot stimulated arterial spasm, resulting in a condition akin to decerebration. Further impedance of circulation with each expiration might account for the increase in rigidity which was such a striking feature of Case 5.

The remaining cases illustrate the occurrence of ischæmic lesions in patients suffering from intracranial lesions.

Case 8.—Aneurysm of anterior communicating artery. Degenerative changes in right precentral cortex. Left-sided flaccid paralysis.

Six days before admission to hospital the patient, a male, aged 47, was found snoring in a chair and could not be roused for a period of ten minutes. He then appeared to waken and continued with his work. Three days later he was brought home from night work in a sleepy, confused state and was said to have been delirious at work. The following day he was "listless and dopey," but as, according to his wife, he was always like this, little notice had been taken of these symptoms. The following day his temperature was 101° F., and influenza was diagnosed. On the morning of admission, however, sleepiness developed into unrousable coma.

Examination revealed left-sided flaccid paralysis. No tendon reflex was elicited, the abdominal reflexes were absent, the right plantar response was equivocal, the left extensor. The systolic blood pressure was 170 mm., the diastolic 90 mm. The retinal arteries were somewhat tortuous. The initial pressure of the cerebrospinal fluid was 290 mm. It was faintly yellow in colour and contained 180 erythrocytes and 8 lymphocytes per c.mm. The protein content was 20 mg. per cent, globulin was not increased. The colloidal gold test showed no precipitation. The Wassermann reaction was negative in cerebrospinal fluid and blood.

The temperature rose, the coma deepened until he died five days after admission to hospital. The cerebral substance between the olfactory tracts was discoloured by blood. There was some thickening of the arachnoid over the convexity and in the basal cisterns. The cerebral sulci of the parietal lobes were widened. Some small patches of atheroma were seen on the basilar artery. The posterior communicating arteries were small and the carotid and middle cerebral arteries were a little thickened. The right anterior cerebral artery was large, and gave rise to a large anterior communicating artery, which was joined posteriorly on the left side by two very small left anterior cerebral arteries, and thence continued forwards as the left anterior cerebral artery. In front of the anterior communicating artery, between the two anterior cerebral arteries, there was a small aneurysmal sac. An aperture on its ventral surface was plugged by blood clot. Only a small quantity of blood had reached the subarachnoid space below; a considerable quantity had passed in the callosal cistern to the cisterna venæ magnæ cerebri. There was no intracerebral blood clot. However, petechial hæmorrhages were seen in the grey matter in the neighbourhood of the right central sulcus, extending from 1·5 cm. to 4 cm. above the sylvian point. Microscopic examination of the motor cortex at a higher level showed early destructive change in the neurones and cellular accumulation in the perivascular spaces. No muscular tissue was to be found in the wall of the aneurysm, which seemed to confirm the diagnosis of a congenital type of aneurysm.

Case 9.—Aneurysm of junction of right anterior cerebral and anterior communicating arteries. Subarachnoid hæmorrhage. Degenerative changes in the territories of right and left anterior cerebral arteries and the right middle cerebral artery. Spastic hemiplegia becoming flaccid, first on one side, then on the other.

A previously healthy woman, aged 70, developed agonizing pain at the top of her head while lifting a heavy bucket of water. She felt giddy and vomited, but did not lose consciousness. Two days later there was marked cervical rigidity and bilateral Kernig's sign. The right pupil was larger than the left. The tendon reflexes were increased on the right side and the right plantar response was equivocal. The blood pressure was 180/100. The cerebrospinal fluid was evenly blood-stained. Five days later she developed spastic paralysis of the left

side, both plantar responses being extensor. On the following day she lost consciousness and the right upper and lower limbs were found to be spastic, and the left limbs flaccid. The cerebrospinal fluid was heavily blood-stained. Three days later the right limbs also became flaccid. During the next eighteen days the patient remained unconscious until pneumonia led to death. The tone of muscles on each side varied from day to day.

The anterior, middle and posterior cerebral arteries were thin walled but the proximal parts showed some patches of atheroma. An aneurysmal sac 4 mm. in diameter was seen at the junction of the right anterior cerebral artery and the anterior communicating artery (fig. 6A). The basal cisterns were stained yellow and some recent blood clot was seen under the olfactory bulbs. The cerebral vessels appeared to be patent throughout. There was patchy degeneration of the medial surfaces of both frontal lobes, of the white matter below the left anterior horn, and more massive disintegration along the upper and lower walls of the sylvian fissure and of the parietal operculum on the right side, as far posteriorly as the trigone of the lateral ventricle (fig. 6B).

The wall of the aneurysm contained no muscular tissue.

It seems probable that these aneurysms were of "congenital" type, in spite of the age of the patient and the presence of atheroma in neighbouring vessels. There was no obvious change in the lumina of the vessels, which were patent and showed no thrombosis. Neither were the infarcts massive. In one case the cerebral change was slight, and in the territory of an artery remote from the aneurysm. In the other, grosser cerebral changes were found in a similar remote zone together with less marked

FIG. 6A.

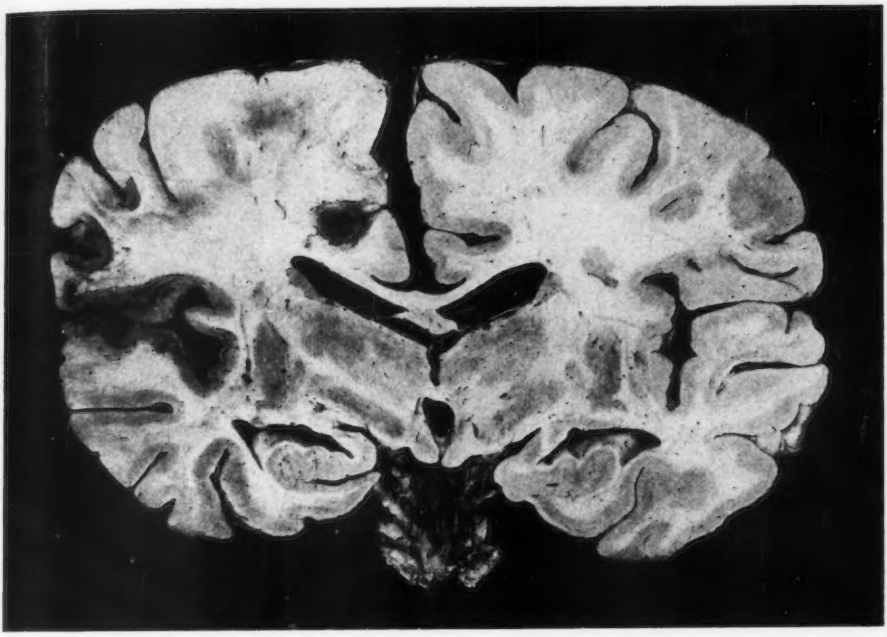

FIG. 6B.

FIG. 6 (*Case* 9).—(A) Aneurysm at junction of right anterior cerebral and anterior communicating arteries. Subarachnoid hæmorrhage. (B) Cerebral infarcts in the absence of intracerebral rupture.

changes in the anterior cerebral zones. Hence, it seems possible that the ischæmic changes were due to temporary spasm of the supplying vessels. The changes in the territories of the anterior cerebral arteries may have been due to compression of the arteries by the aneurysm, but it is more likely that the latter stimulated spasm of the vessels, even of vessels remote from the aneurysm. Such spasm of arteries concerned in collateral circulation has been observed following trauma to arteries in limbs. In another case with localizing signs, the anterior cerebral arteries of the fixed specimen were obliterated in the blood clot between the frontal lobes. It is difficult to state whether compression existed during life, but the observation raises the possibility of obliteration of the lumen by contraction of blood clot. In some cases thrombosis or embolism may produce cerebral damage but no definite evidence of these causes was found in the cases examined.

It is of interest that the cerebral damage followed subarachnoid hæmorrhage in each case, but it is conceivable that an apparent cerebral thrombosis might be due to the presence of an aneurysm which escaped

FIG. 7 (*Case* 10).—Aneurysm of anterior communicating artery rupturing into the left frontal lobe. Infarct in right frontal lobe.

detection. It is probable that this mechanism of cerebral damage is much more frequent than is suspected. Fig. 7 demonstrates hæmorrhage into one frontal lobe, and ischæmic changes of the other, in a patient, Case 10, aged 24, with an aneurysm of the anterior communicating artery, and otherwise normal arteries.

Three further cases, occurring later than the consecutive series and not included in the post-mortem series, may be briefly mentioned in order to make the picture more complete.

Case 11.—Aneurysm of anterior cerebral artery. Intracerebral rupture without abnormal reflexes.

A large blood clot was demonstrated in the postero-inferior portion of a frontal lobe, deforming the anterior horn. Notwithstanding, daily search failed to reveal abnormal motor signs, except for generalized weakness of limbs.

Case 12.—Subacute bacterial endocarditis. Mycotic aneurysm of middle cerebral artery. Rupture into frontal and temporal lobes.

A young woman suffered from subacute bacterial endocarditis. The infection was inhibited, but not cured, by 2½ million units of penicillin daily. Death was produced rapidly by the rupture of a mycotic aneurysm of the middle cerebral artery. Lying in the sylvian fissure, it caused a massive effusion of blood into the temporal and frontal lobes.

Thus, mycotic aneurysms may lead to cerebral damage and it is conceivable that death might occur even when the invading organism is completely destroyed. A study of other such cases suggests that inflammatory changes around the aneurysm may predispose to intracerebral rupture. Thus, two mycotic aneurysms situated on the convexity caused extensive cerebral damage after rupture.

Case 13.—Aneurysm of middle cerebral artery. Rupture into temporal lobe. Hemiplegia and oculomotor paralysis.

A woman, aged 47, while eating, suddenly complained of terrific pain at the back of her head and neck. Within ten minutes she appeared to be delirious, saying "Oh, my head, my head." Her right eyelids closed within ten minutes of the onset of the pain and her left limbs were noticed to be weak. On admission to hospital, four days after the onset, she was extremely ill, with a temperature rising

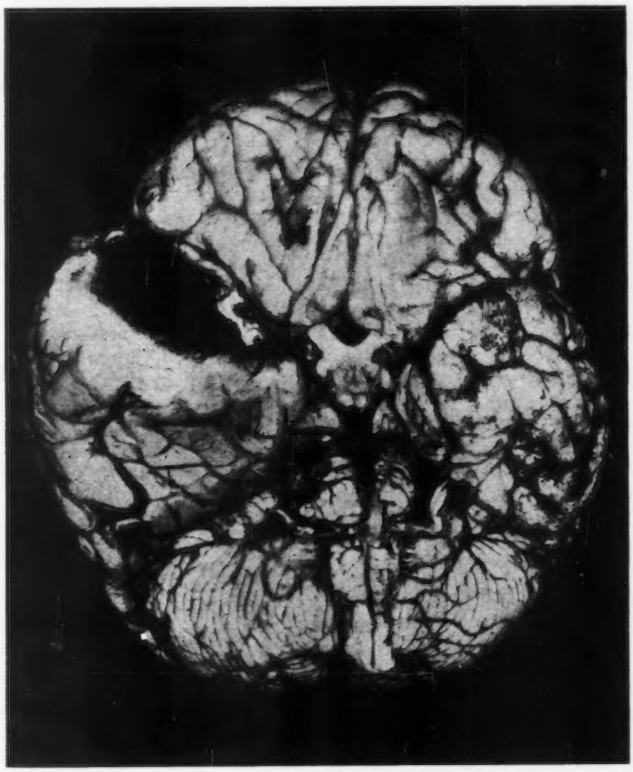

FIG. 8 (*Case* 13).—Aneurysm of middle cerebral artery with rupture into the right temporal lobe. In addition to left hemiplegia there was right oculomotor paralysis, presumably due to pressure upon the nerve in the incisura tentorii exerted by the distended temporal lobe.

to 103° F., rapid respiration and signs of pulmonary consolidation. In addition to signs of meningeal irritation, there was complete right oculomotor palsy, and left hemiparesis. The left-sided deep reflexes were diminished and the plantar response was extensor. The abdominal reflexes were absent on both sides. The cerebrospinal fluid was under an initial pressure of 10 mm. It contained 3,000 erythrocytes per c.mm. and the supernatant fluid was yellow. The pulmonary infection advanced in spite of treatment with penicillin and sulphadiazine and she died nine days after the onset.

A small aneurysm was found on the right middle cerebral artery in the sylvian fissure (fig. 8). It was embedded in blood clot which occupied a ragged cavity in the temporal lobe, which was distended with blood clot. Blood had burst internally into the temporal horn. The uncinate gyrus was large and grooved by the free edge of the tentorium, suggesting that the oculomotor palsy was due to compression of the nerve caused by the enlarged temporal lobe in the incisura tentorii.

Thus, it is necessary to remember that false localizing signs may be produced by intracerebral rupture. This is especially important in connexion with surgical approach.

Case 14.—Aneurysm of middle cerebral artery. Rupture into temporal lobe. Coma, with remarkable ability to recall events when roused, hemiplegia, hemianopia, slight sensory loss, bilateral 3rd nerve palsy. Incisural herniation.

A married woman, aged 37, suddenly experienced terrific pain in the right temporal region, which spread through the right side of the head to the occipital region, and then down the neck and between the shoulder blades. The headache continued until she became comatose fourteen hours after the onset. Thereafter, her husband noticed that the left limbs remained immobile, although the right limbs were moved restlessly. During the third and fourth days brief attacks of twitching of the left side of the face and left arm occurred. On the fifth day respiration was periodic. She could be roused temporarily when respirations were deep. During these periods she was able to describe the headache fully, and gave a detailed account of family excitements which she thought responsible for her attack. Even though consciousness lapsed many times during her account, she took up the thread where she had left off on each occasion.

It was possible to carry out physical examination by repeatedly arousing the patient, and for short periods she was able to co-operate in a drowsy fashion. There was left-sided homonymous hemianopia. The edges of the optic discs were blurred. The right pupil was larger than the left, and both reacted very feebly to light. Adduction and upward rotation of the right eye were only feebly present, of the left eye slightly defective. There was gross bilateral ptosis, more marked right than left. Abduction of the right eye was not quite complete, abduction of the left eye was still more defective.

There was marked weakness of the left lower facial musculature. She appeared to be unable to flex or abduct the left shoulder, or to abduct the fingers; other movements of the left upper limb were feebly present. Movements of the left lower limb were considerably stronger than those of the arm, but were weak compared with those of the right limb. The tone of the adductors of the left shoulder appeared to be increased, but elsewhere muscles were hypotonic.

The deep reflexes were all reduced, but appeared to be equal on the two sides. The superficial abdominal reflexes were absent; the plantar responses difficult to elicit. Firm stimulation of the lateral border of the right foot produced feeble flexion; of the left, extension.

The point of a pin was appreciated as such on the left side, but felt blunter than

on the right. Stereognosis was inaccurate from the left hand, but accurate on the right.

There was marked cervical rigidity and slight Kernig's sign on both sides. The pulse rate was 80, the blood pressure 130/90.

The cerebrospinal fluid was yellow in colour and turbid, the initial pressure being 350 mm. 6 c.c. of fluid was removed, the pressure falling to 120 mm. The patient could not be roused for about an hour after the puncture. Subsequently she improved to a state comparable to that before the puncture, and remained so for about twelve hours, when respiratory and cardiac failure occurred in rapid succession.

A diagnosis of aneurysm of the right middle cerebral artery with subarachnoid hæmorrhage and, later, rupture into the temporal lobe seemed to be indicated by the sequence of events. The remarkable preservation of power of recall of recent memories when roused from coma may be a helpful sign in distinguishing hæmorrhage into central white substance from ischæmic lesions of the middle and anterior cerebral arteries. The preponderance of motor over sensory signs also suggested the presence of a hæmorrhage affecting the descending motor fibres, rather than obstruction to the middle cerebral artery, for the latter would presumably cause severe sensory loss. The lack of gross sensory loss in the presence of marked motor and visual loss suggested that the hemianopia was due to involvement of the optic tract or optic radiation, rather than to a purely capsular lesion. The presumptive position of the aneurysm suggested involvement of the tract. The occurrence of motor convulsions also suggested that the descending motor fibres were intact.

There can be no doubt that lumbar puncture is dangerous in such a case. The findings suggested the presence of a space-occupying lesion in the right hemisphere, and the impairment of both oculomotor nerves (especially the right) gave evidence of the presence of uncinate herniation and compression of the nerves in the incisura tentorii. The weakness of the external recti was probably due to stretching of the 6th cranial nerves. Withdrawing fluid from below undoubtedly increased the crowding into the incisura. This point may justify the controversy which has arisen regarding the advisability of lumbar puncture in subarachnoid hæmorrhage. When the blood has passed only into the subarachnoid space the pressure is transmitted equally throughout, as in any hydrostatic system. In such instances when fluid is able to flow freely from the supratentorial region to the lumbar theca, withdrawal of fluid will reduce the pressure in the skull as much as in the lumbar theca. When, however, a mass of clot has increased the bulk of the hemispheres above the tentorium the possibility of incisural and foraminal herniation are just as great as in cases of neoplasm. At all events there is a very great contrast between the deterioration of this patient's condition and the relief which usually follows lumbar puncture in uncomplicated subarachnoid hæmorrhage. It

is possible that those who condemned lumbar puncture in subarachnoid hæmorrhage had unfortunate experiences in which unsuspected intracerebral hæmorrhage had occurred. The next case serves as a further warning, for a marked cerebellar pressure cone occurred with an ischæmic lesion.

The clinical diagnosis was substantiated by the post-mortem findings (fig. 9). There was an unusual broadening of the middle cerebral artery

FIG. 9 (*Case* 14).—Aneurysm of middle cerebral artery with rupture into the temporal lobe. Note the notching of the right 3rd nerve and the acute kinking of the left 3rd nerve around the posterior cerebral artery.

in the stem of the sylvian fissure, where the parent vessel divided into three large branches. Here a gap was found in the lower wall, presumably representing the point of attachment of an aneurysmal sac. The anterior portion of the temporal lobe was disintegrated and a ragged cavity containing blood extended deeply, upwards and medially, through the temporal lobe to abut upon the lateral wall of the trigone of the lateral ventricle, reaching as high as the roof of the body of the ventricle. Although in such close contact, no breach was made in the wall of the ventricle. The internal capsule and basal ganglia were intact above and in front of the cavity. Rupture had occurred into the circular sulcus of Reil which contained a large clot. It appeared, therefore, that the hemianopia was due to interruption of the visual radiation lateral to the

trigone—an interesting example of the extensiveness of such intracerebral lesions.

This case, therefore, demonstrates a number of important points: (i) The symptomatology of intracerebral rupture of aneurysms of the middle cerebral artery; (ii) the mechanism of 3rd nerve palsy as a false localizing sign of aneurysm; (iii) the inadvisability of lumbar puncture when intracerebral rupture has occurred.

Case 15.—Aneurysm of distal part of internal carotid artery. Spasm of anterior cerebral arteries. Paralysis of one side of the body, with little alteration of tone and deep reflexes. Reflex grasping in opposite hand. Absent abdominal reflexes and extensor plantar responses. Cerebellar pressure cone.

A peculiar cry caused her husband to rush upstairs to find the patient on her hands and knees. She said, "Get the doctor, I'm dying, my head's bursting." He lifted her to bed, where she vomited a number of times, and complained bitterly of her head. The headache diminished during the next few days. However, five days after the onset she had difficulty in speaking, her left upper eyelid drooped and she was unable to move her right arm and leg. She became unconscious some hours later.

On admission to hospital six days after the onset it was possible to rouse her for brief intervals, although she made no verbal response. There was complete bilateral ptosis. The left pupil was larger than the right, and both reacted very feebly to light. The right corner of the mouth did not move, and spontaneous movements were observed only in the left limbs. Pricking with a pin caused movement of the left arm and left lower limb, and slight movement of the right foot, but no movement of the right arm. There was an increased resistance to flexion of the right elbow, but no increase was noticed at the wrist. Manipulation of the left limbs sometimes encountered resistance, but at times the muscles appeared flaccid, especially when manipulation was gentle. There was brisk reflex grasping in the left hand. No definite alteration was noted in the tone of the lower limbs. The tendon reflexes of the right upper limb were brisk, and elsewhere were diminished. The superficial reflexes were absent, the plantar responses briskly extensor, especially on the right. Signs of meningeal irritation were present.

The suggested diagnosis was aneurysm of the anterior communicating or left anterior cerebral artery, with rupture into both frontal lobes. It was thought that the 3rd nerve lesion might have been due to involvement in the incisura tentorii. However, the possibility that the frontal lesion was due to spasm was also considered. The patient's clinical condition deteriorated rapidly, and she died forty-eight hours after the onset of the hemiparesis. Lumbar puncture was avoided because of the previously recorded experience.

There was a thin-walled aneurysm growing from the left internal carotid artery just below the point of origin of the posterior communicating artery (fig. 10). There was no doubt of the separation of the neck of the sac and the division of the parent trunk. The lower part of the wall was adherent to the corresponding anterior clinoid process, and the sac tore during removal. There was some subarachnoid hæmorrhage, and a small clot was present in the left sylvian fissure. There was a gross degree of depression of the cerebellar tonsils. A tiny unruptured aneurysm was seen at the first bifurcation of the right middle cerebral artery. Otherwise the middle cerebral arteries appeared normal. No intracerebral rupture had occurred. There was, however, an area of disintegration of the lower part of the left frontal lobe, extending deeply into the lobe as a wedge-shaped area with its apex abutting upon the frontal horn. The cortex of a corresponding area of the medial surface of the right frontal lobe showed slight degenerative change. The anterior cerebral arteries contained blood proximal to the anterior communi-

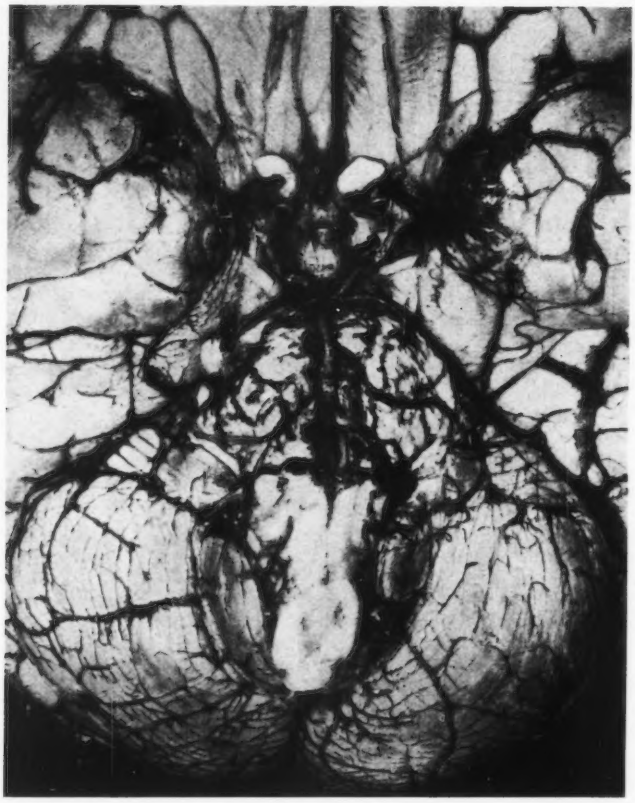

FIG. 10 (*Case* 15).—Aneurysm of internal carotid artery. Cerebellar pressure cone. Liquefaction of anterior part of left frontal lobe, milder degenerative changes in the right frontal lobe.

cating artery, but, distally, they appeared unusually small and were devoid of blood. The ischæmia was probably due to spasm of the anterior cerebral arteries.

The 3rd nerve palsy may have been due to the direct pressure of the aneurysm, for it was in close contact with the nerve. The reason for the cerebellar pressure cone was obscure. No swelling of the brain was apparent, nor was there any large collection of blood in the brain or subarachnoid space. It seems probable that there was gross œdema as an initial reaction to ischæmia, but, if so, this had rapidly disappeared.

This case illustrates that

(1) It is difficult, and sometimes impossible, to differentiate between the intracerebral hæmorrhage and ischæmic lesions, although the involved vessel can be forecast.

(2) Ischæmic lesions may be due to arterial spasm. (Review of the available material suggests that such ischæmic lesions are not rare,

although far less common than intracerebral hæmorrhage. The vessel involved may be remote from the aneurysm.)

(3) Lumbar puncture may be dangerous in ischæmic lesions as well as after intracerebral hæmorrhage.

Analysis of Ninety-three Post-mortem Records

The fact that 10 cases were observed consecutively produced an ineradicable, although possibly fallacious, impression of the importance of intracerebral rupture. In order to obtain further information a review was made of the post-mortem records of the Royal Melbourne Hospital.

Intracranial aneurysms were found in 93 autopsies conducted at the Royal Melbourne Hospital between 1919 and September, 1947. In the 93 patients, 99 aneurysms were found. (Two aneurysms were present in each of 4 patients, and in another, three aneurysms were encountered.) Included in this number were at least four aneurysms due to dilatation of atheromatous vessels, and three mycotic aneurysms. Massive intracerebral hæmorrhage, usually reaching the ventricular system, was present in 56. In 9, there was more superficial destruction of cerebral tissue. Ischæmic infarcts are described in 5 patients. This number includes 3 patients here described. It seems probable that infarcts occur more frequently than the total figure suggests, this complication possibly escaping detection when the brain is examined without fixation. In nearly all of these patients, blood was also present in the subarachnoid space. Subarachnoid hæmorrhage alone was present twenty-eight times.

The material is analysed more fully in Table I.

Table I.—Analysis of Frequency of Intracerebral Hæmorrhage and Subarachnoid Hæmorrhage

Deaths :	93	
Total number of aneurysms of all types		99
Cerebral damage		65
Massive intracerebral hæmorrhage		56
Superficial destruction		9
Subarachnoid hæmorrhage alone		28
Ischæmic infarcts		5
Atheromatous aneurysms :	4	
Intracerebral hæmorrhage		3
Subarachnoid hæmorrhage alone		1
Mycotic aneurysms :	3	
Intracerebral rupture		2
Subarachnoid hæmorrhage alone		1
Congenital aneurysms :	92 in 86 patients	
Intracerebral hæmorrhage		60
Massive hæmorrhage		51
Superficial destruction		9
Subarachnoid hæmorrhage alone		26

The relationship between the position of the aneurysm and the result of rupture is analysed in Table II.

TABLE II.—POSITION OF CONGENITAL AND ATHEROMATOUS ANEURYSMS AND EFFECT OF RUPTURE

Parent artery	*Number of aneurysms*	*Subarachnoid hæmorrhage alone*	*Intracerebral hæmorrhage*	*Position and extent of cerebral damage*
Anterior cerebral (Those growing from point of junction of anterior cerebral and anterior communicating arteries are included in next group)	7	1	6	3 ruptured into frontal lobe on corresponding side 1 ruptured into one frontal lobe and corpus callosum 1 caused superficial erosion of both frontal lobes 1 caused superficial erosion of one frontal lobe
Anterior communicating	34		29	6 ruptured into one frontal lobe 1 ruptured into one frontal lobe and corpus callosum 3 caused superficial erosion of one frontal lobe 1 caused superficial erosion with destruction of genu of corpus callosum 1 caused superficial erosion and rupture into 3rd ventricle 15 ruptured into both frontal lobes 2 ruptured into both frontal lobes and anterior part of corpus callosum

TABLE II. (*contd.*)—POSITION OF CONGENITAL AND ATHEROMATOUS ANEURYSMS AND EFFECT OF RUPTURE

Parent artery	*Number of aneurysms*	*Subarachnoid hæmorrhage alone*	*Intracerebral hæmorrhage*	*Position and extent of cerebral damage*
Termination of internal carotid artery	5	2	3	1 ruptured into frontal lobe 1 ruptured into the thalamus 1 caused erosion of temporal lobe (paralysis of the 3rd nerve also present)
Middle cerebral artery from its commencement to the 1st large branch	29	8	21	4 ruptured into frontal lobe 4 ruptured into parietal lobe 1 ruptured into frontal and parietal lobes 1 ruptured into parietal and occipital lobes 6 ruptured into temporal lobe 2 ruptured into temporal lobe and basal ganglia 3 caused erosion of temporal lobe
Beyond 1st branch	3		3	2 ruptured into insula 1 ruptured into temporal and parietal lobes
Junction posterior communicating and internal carotid arteries	3	3		
Junction posterior cerebral and posterior communicating arteries	1		1	1 ruptured into temporal lobe

TABLE II. (*contd.*)—POSITION OF CONGENITAL AND ATHEROMATOUS ANEURYSMS AND EFFECT OF RUPTURE

Parent artery	*Number of aneurysms*	*Subarachnoid hæmorrhage alone*	*Intracerebral hæmorrhage*	*Position and extent of cerebral damage*
Bifurcation of basilar artery	1	1		
Posterior cerebral artery	4	2	2	1 ruptured into the thalamus 1 ruptured into posterior temporal and occipital lobes
Junction basilar arteries	1	1		
Origin posterior inferior cerebellar artery	1	1		
On posterior inferior cerebellar artery	1	1		

Three mycotic aneurysms were present upon smaller branches of the anterior and middle cerebral artery over the surface of the cerebral hemisphere. Blood reached the lateral ventricle through the parietal lobe in one patient and through the occipital lobe in another.

Thus it is seen that aneurysms of the anterior cerebral and anterior communicating arteries, lying between the medial surfaces of the frontal lobes, tend to rupture into the substance of one or both frontal lobes Aneurysms along the course of the middle cerebral artery, especially where they lie in the sylvian fissure between frontal and temporal lobes, rupture with equal frequency into the frontal and temporal lobes. Within the temporal lobe, blood may extend to the temporal horn, to the basal ganglia and to the internal capsule. Less frequently blood extends upwards into the parietal lobe, and a massive effusion may reach even to the occipital lobe.

None of six aneurysms of the posterior communicating artery caused cerebral damage. However, the only aneurysm growing from the junction of the posterior communicating and posterior cerebral artery ruptured into the temporal lobe. The posterior cerebral artery differs from the posterior communicating artery in being surrounded by pial-covered cerebral surfaces, where it lies under cover of the medial part of the temporal lobe. Of four aneurysms upon this vessel, one ruptured into the thalamus, and one into the posterior part of the temporal lobe and into the occipital lobe.

Manifestations of Intracerebral Rupture

The patients were usually admitted to the general wards of the hospital in a shocked, irritable or comatose condition, hence the clinical records were often lacking in detail. However, the following information was gleaned:

Rupture into one frontal lobe.—In most instances there was contralateral flaccid hemiparesis with diminished tendon reflexes and an extensor plantar response. Frequently both plantar responses were extensor. The degree of weakness was sometimes marked soon after the onset, but later was only slight. In some patients the deep reflexes became more active and the tone increased, a state which usually followed one of flaccidity. The head and eyes were sometimes turned towards the unparalysed side. Fits occurred in 4 patients out of a total of 21, with gross destruction and more superficial erosion. In one the head and eyes were deviated to the weak side, then twitching of the contralateral facial muscles commenced and spread to the limbs on the corresponding side of the body. In a second there was contralateral spasm, in a third the arm only was affected. In a fourth (Case 1) there were attacks characterized by marked opisthotonus, with rigid extension of the contralateral arm and of the lower limbs, the ipsilateral arm being rigidly flexed. The limbs were flaccid in between the attacks. This may have been due to the blood clot over the brain-stem.

Rupture into both frontal lobes.—The patients were usually comatose but some retained consciousness throughout. In the initial stages bilateral flaccidity of weak or immobile limbs was noted, with diminished or absent deep reflexes, absent abdominal reflexes and extensor plantar responses. In some few cases the limbs were spastic with increased deep reflexes.

Fits were present in 3 of the 18 patients with bilateral frontal damage. In one patient (Case 3) bilateral tonic and clonic convulsions occurred, while in one attack the twitching commenced on one side before becoming generalized. In a second patient the head and eyes deviated strongly to the left, the right elbow was extended and the shoulder internally rotated while the left arm twitched. Subsequently it was noted that all limbs were spastic. In the third patient (Case 5) the attacks were characterized by rigid extension of the abducted upper limbs, with flexion or mild extension of the wrists, the hands being partly closed. Accesses of tone occurred during each expiration, producing forced movement of the arms in the manner indicated. The lower limbs were rigidly extended with inverted feet throughout. The attacks lasted for some minutes and recurred frequently during the last hour of life. In this patient there was massive blood clot over the brain-stem.

In most of these patients one or both pupils were usually dilated and

failed to react to light. The pupillary signs do not appear to give evidence of the side of the lesion. In those cases which survived the initial insult, the weakness usually lessened, but when paresis remained the muscular tone increased. In those with very extensive destruction initial profound dementia lessened to moderately severe reduction of higher cerebral faculties. In one case the limbs opposed passive manipulation in all directions, the increase being encountered more strongly the more forcible the manipulation, and appeared equal in flexors and extensors alike. In this patient reflex grasping could be elicited in each hand.

It is probable that the effect upon voluntary movement depends upon whether the blood remains confined to the lower and posterior part of the frontal lobe, whether it extensively disrupts one or both hemispheres, or whether it exerts compression upon the descending motor fibres. In the former case the effect may be surprisingly slight (although the illness lasts longer than in the case of purely subarachnoid effusion). When the frontal lobes are extensively destroyed the paresis may diminish if the patient survives, but evidence of damage to the frontal lobe may persist. When the pyramidal fibres are compressed or destroyed the hemiparesis will approximate to that of a capsular lesion and will also probably diminish, especially when due to compression, if the patient survives.

Destruction of genu of corpus callosum.—Such damage was usually associated with hæmorrhage into the frontal lobes. In one patient, however, there was but superficial erosion of frontal tissue. In this patient the head and eyes were deviated to the left and the left arm and leg were weak.

Involvement of internal capsule.—When the internal capsule was destroyed there was flaccid hemiplegia during the unconscious period. If survival occurred, the tone of the paralysed limbs increased, and hemianæsthesia and hemianopia were found. No fits were observed.

Rupture into temporal lobe.—In a considerable portion contralateral facial paralysis was obvious and sometimes flaccid hemiparesis (less marked than the facial paralysis). In a lesser number the deep reflexes were increased. In a considerable proportion the plantar response was extensor on both sides. A number of patients were aphasic. In only one patient was hemianopia noted. The clinical state of most of these patients discouraged attempts at examination of the visual fields.

Fits were present in 2 of a series of 15 patients. In one, convulsive movements were unilateral, in a second, confined to the opposite corner of the mouth, and in a third were generalized.

Rupture into parietal lobe.—Flaccid hemiplegia was noted. The state of the patients apparently precluded testing of sensation.

Rupture into thalamus.—In one case an aneurysm of the posterior cerebral artery ruptured into the thalamus and thence into the lateral

ventricle. The patient was deeply comatose and respiration was of Cheyne-Stokes' type. The spine was extended and arched. The upper limbs were rigidly extended with flexion of the wrists and fingers. The lower limbs were rigidly extended and adducted. The deep reflexes could not be elicited because of the extreme rigidity. The abdominal reflexes were absent and the plantar responses were extensor. The ventricles were filled with blood. The post-mortem record makes no mention of the presence of blood clot over the brain-stem, but refers to the presence of blood clot in the subdural space. It is conceivable that hæmorrhage into the thalamus in this position might itself produce a state of decerebration.

Prognosis of Intracerebral Rupture

Although cerebral damage makes the prognosis more serious, a number of patients recovered whose signs suggested the presence of considerable cerebral damage. Minor changes in reflexes were noted in some of the patients who recovered, and gross mono- or hemiparesis were present in 18 per cent.

More careful observation and examination of such cases will undoubtedly produce fuller and more accurate evidence of localization. However, judgment of this point is complicated, for it is not possible to assert that hemiplegia is evidence of intracerebral rupture. It may be a temporary or permanent effect induced by ischæmia. Such signs may exist without damage to the brain obvious at autopsy.

Localizing Signs in the Absence of Intracerebral Hæmorrhage: Cerebral Ischæmia

A considerable proportion of the cases in which post-mortem examination failed to reveal macroscopic cerebral damage exhibited localizing signs and convulsions during the terminal illness. It is probable that cerebral damage remained undetected in a number of the post-mortem series described. Ischæmic changes were seen in 3 of the 10 cases personally examined, but were recorded in only 2 of the far larger number examined without previous fixation. Nevertheless, localizing signs have been observed when careful search fails to reveal macroscopic cerebral damage. The signs may be considered in relation to the artery affected:

Aneurysm on the anterior cerebral artery: In one patient, without cerebral tearing, the pupils were dilated and fixed, the limbs were flaccid and the plantar responses equivocal in type.

Aneurysms on the anterior communicating artery: Of 9 patients without cerebral damage, fits occurred in 2. In each there were attacks characterized by intermittent forcible flexion of the upper limbs, followed by forcible extension of the lower limbs. The plantar responses were

extensor on both sides. In 4 other patients, the deep reflexes were recorded as being diminished. Abnormalities of the pupillary reflexes were common.

Aneurysms on the middle cerebral artery: In 6 patients the following signs were noted. The pupil was larger on the side of the aneurysm in some cases, sometimes on the other. Deep reflexes were absent in 5 patients, increased in 1. There was no plantar response in 3: it was extensor on both sides in 2 patients and on the opposite side in 1 patient. There was mild hemiparesis in 1 patient. 2 patients suffered from convulsions of the opposite side of the body.

Aneurysms on the posterior communicating artery: Paresis of the 3rd, 4th and 6th cranial nerves was present in 2 cases. The plantar responses were equivocal in one case, extensor in another and absent in a third. One patient suffered from flexor spasms of the arms, with extensor spasms of the lower limbs, the feet being inverted and plantar flexed.

Aneurysms on the posterior cerebral artery: The cerebral tissues escaped obvious damage in one aneurysm of the left posterior cerebral artery. In this case the pupils were dilated and fixed. The right facial muscles and right upper limb were weak, the tendon reflexes were absent on the right side and both plantar responses were extensor.

Thus, hemiparesis, convulsions and phasic disorders of tone may occur when escaping blood passes only into the subarachnoid space. It is probable that the localizing signs are due to spasm of arteries, of insufficient duration to produce permanent cerebral damage. In other cases death may occur before the ischæmic changes are sufficiently marked to be seen macroscopically. It is probable that this mechanism is far commoner than realized. In such cases, microscopic examination might well be repaid.

The suggestion that such localizing signs are due to ischæmia in the territory of the parent vessel receives some support from a comparison of the signs and convulsive disorders produced by aneurysms, of the various arteries, which ruptured intracerebrally. No definite difference in the quality of the signs is to be observed. However, it is to be remembered that the cerebral changes promoted by ischæmia may be remote from the territory of the artery bearing the aneurysm (Case 8).

Differentiation of Intracerebral and Subarachnoid Rupture

An attempt was made to determine whether there was any significant divergence between the clinical course of patients with intracerebral rupture and subarachnoid hæmorrhage.

A comparison of the duration of life of patients who died as the result of rupture of intracranial aneurysms showed that a considerably greater

percentage of patients died within the first twenty-four hours than on any subsequent day, whether the rupture was intracerebral or into the subarachnoid space. The percentage, however, was much greater in the latter group. The figures for the whole of the first week showed a slighter preponderance of those with subarachnoid hæmorrhage alone. In contrast, a higher percentage died with intracerebral hæmorrhage during the second week. The number of deaths at subsequent periods was smaller and the figures unreliable once the patient was discharged from hospital.

A review of the histories of the two groups failed to reveal any marked difference in symptomatology. Those with intracerebral hæmorrhage lost consciousness without initial complaint of headache more frequently than those with subarachnoid hæmorrhage alone. Localizing signs and symptoms were more frequent in the former group, as has already been discussed. The temperature appears to rise earlier and abruptly, and sometimes to a high level, when hæmorrhage occurs into the frontal lobes. Otherwise no significant difference was noticed in the temperature charts.

Thus, it may be said that differentiation between the two groups is far from absolute. However, clinical experience suggests that, although mistakes may be made, it is usually possible to determine whether intracerebral rupture has occurred and to suggest, in some cases, the vessel affected by the aneurysm.

Factors Determining Intracerebral Rupture

Undoubtedly the biggest factor in the production of cerebral laceration is the position of the aneurysm. Aneurysms of the arteries which lie free upon the base of the brain tend to rupture into the subarachnoid space; those lying between cerebral surfaces frequently rupture into the brain. Thus, the common sites of intracerebral rupture are between the two frontal lobes and in the sylvian fissure. The posterior cerebral artery may also bleed into the brain. In such situations the position of the rupture and its size are important factors, determining whether the escaping stream of blood will impinge upon the brain, and the force with which it does so. Adhesions around the aneurysm sealing it off from the subarachnoid space, resulting perhaps from previous rupture, may also contribute to cerebral damage. Inflammatory sealing-off may be prone to occur with mycotic aneurysms, thus explaining the frequency with which mycotic aneurysms lying upon the convexity rupture into the brain.

Sometimes the aneurysm becomes embedded in cerebral tissue during its gradual expansion. This probably occurred in Cases 1, 2 and 7, and is further demonstrated in fig. 11. This aneurysm, embedded in the medial portion of the temporal lobe caused uncinate epilepsy and serves as a reminder that focal epilepsy may occur apart from rupture. Aneurysms

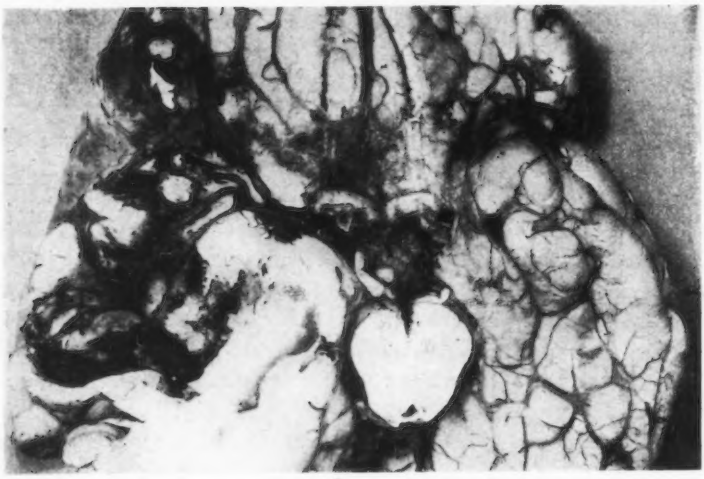

FIG. 11.—Leaking aneurysm of the middle cerebral artery embedded in the temporal lobe.

of the termination of the internal carotid, growing above the obtuse angle of junction of the anterior and middle cerebral arteries, are prone to become embedded in cerebral tissue and hence rupture with some frequency into the brain, although the parent arteries lie freely within the subarachnoid space.

SUMMARY

Intracerebral rupture of intracranial aneurysms is of frequent occurrence, whether the aneurysm be "congenital," atheromatous or mycotic.

The clinical features may serve to indicate the occurrence of intracerebral rupture, and the presenting signs may indicate the site of the lesion, but mistakes are possible. Rupture of aneurysms of the anterior cerebral or anterior communicating arteries may lead to bilateral motor involvement, the muscles usually being flaccid and weak. In later stages the tone tends to increase. When the blood has passed directly to the inferior aspect of the frontal horns, the patient may show little evidence of intracerebral rupture. In some cases, if the lesion is bilateral and very extensive, "tonic innervation," reflex grasping and dementia may be apparent. Localization is more difficult when the manifestations are predominantly on one side. In the early stage of flaccid hemiparesis it may be difficult to determine whether rupture has occurred into one frontal lobe from an aneurysm upon the anterior cerebral, anterior communi-

cating, or middle cerebral artery, or into the temporal lobe. Rupture into the temporal lobe may produce greater weakness of the face than of the limbs. Analysis of the type of speech defect, when present, may help in localization. When the hæmorrhage involves the internal capsule the surviving patient shows sensory and visual, as well as motor, involvement. Fits occur with considerable frequency and may be generalized with tonic and clonic spasm, or may be of localizing value. In frontal lesions the arm or arm and face may alone be involved. When the temporal lobe is affected the facial muscles only may twitch. However, much larger numbers must be observed before the accuracy of any such general statements can be claimed. Tonic fits with rigid extension of upper and lower extremities, with or without opisthotonus, were observed to occur in cases in which there was much blood clot over the ventral surface of the brainstem. No fits occurred in the cases in which the internal capsule was destroyed.

Intracerebral rupture is not the only cause of hemiplegia and fits. Ischæmic changes have been observed in the brain, sometimes in vascular territory remote from that of the vessel bearing the aneurysm. Spasm of arteries appears to be the probable cause.

In some cases, hemiplegia may be due to pressure exerted by blood clot, rather than to cerebral destruction. In these cases evacuation of the clot may lead to recovery.

The prognosis of intracerebral rupture is worse than that of massive subarachnoid hæmorrhage, although death tends to occur more rapidly in the latter.

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QUANTITATIVE OBSERVATIONS ON THE OLFACTORY SYSTEM OF THE RABBIT

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DURING the course of a morphological study of the rabbit's olfactory system a number of quantitative observations have been made. Some of these are recorded here because they have a bearing on two problems: first, the numerical relationship of the primary olfactory neurons (in the olfactory epithelium and nerves) to the secondary olfactory neurons (in the olfactory bulbs), a relationship which is of importance in any consideration of the structural basis of olfactory discrimination, and, secondly, the contribution which each of the different cell-types in the olfactory bulb makes to the olfactory tract.

Few quantitative data for the various elements in the olfactory system are available. Holt (1917) counted 75,000 mitral cells in each olfactory bulb of Norway rats. L. A. Smith (1928) compared the number of mitral and internal granular cells in wild Norway and domesticated albino rats; he gave an average estimate of about 3,200,000 internal granular cells and 55,000 mitral cells in the albinos, and 5,600,000 granular cells and 37,000 mitral cells in the wild specimens. However, these figures for mitral cells are in all probability too high, because other cell-types appear to have been included in the counts. The number of glomeruli in the human olfactory bulb is given as about 10,000 by C. G. Smith (1940), but, as he made no allowance for the appearance of one glomerulus in several successive serial sections, the figure which he gives is much too high also. No attempt has hitherto been made to collect more complete data for any one species.

It is hardly necessary to point out that there are numerous sources of error in estimations of this nature; in our study we have tried to eliminate as many of these as possible. However, the figures given cannot be regarded as more than approximations: to obtain accurate results which take into account the normal range of variability, it would be necessary to examine much more material than we have had at our disposal.

MATERIAL

The rabbits used in this study were for the most part between 3 and 4 months of age. In older laboratory animals there is a high incidence of chronic atrophic rhinitis, and a great deal of our material prepared from

rabbits older than 6 months is useless because of inflammatory changes in the olfactory mucous membrane.

In 2 cases the anterior part of the skull had been removed intact, fixed in formalin, decalcified, embedded in celloidin, sectioned serially at 15 μ (one in a transverse and one in a sagittal plane), and every 33rd section stained with hæmatoxylin and eosin. These sections were used to estimate the surface area of the olfactory epithelium.

No significant differences in thickness and cell density between the olfactory mucous membrane lining the nasal septum and that lining the ethmo-turbinals were observed in these specimens, so in subsequent studies of the olfactory epithelium that part which lies on the septum was taken as representative of the whole. Because most of the septum is cartilaginous, it can be sectioned without the inconvenience of decalcification, which interferes with later treatment of the tissues with delicate techniques of silver impregnation. In a number of young rabbits, the nasal septum was fixed by perfusion through the aorta with 70 per cent alcohol, and series of 10 μ paraffin sections, transverse and tangential to the mucous membrane, prepared by the protargol method (Bodian, 1936). From measurements made immediately after death, and subsequently when the material was blocked, it appeared that there was very little shrinkage (possibly because of the firm cartilaginous support of all the tissues): for this reason, no corrections for shrinkage are made in the counts of olfactory receptors for which these preparations were used.

Eight series of 15 μ sections through olfactory bulbs of rabbits of comparable age were also available. These series were taken in transverse and sagittal planes: four had been impregnated with protargol after perfusion with 70 per cent alcohol, and four had been stained with Borrel's methylene blue after immersion in absolute alcohol and acetic acid. Counts of the various cells in the olfactory bulb and of the fibres in the olfactory tract were made from these sections.

Since the way in which such estimations are carried out determines the accuracy of the figures obtained, in this communication methods are in each case described in the appropriate sections along with results. In all cases only the main olfactory bulb, and not the accessory bulb, was studied.

Preliminary Anatomical Outline

The olfactory receptors in the rabbit have been recently described by Le Gros Clark and Warwick (1946). They are small bipolar nerve cells with stout peripheral processes, or olfactory "rods," which extend to the surface of the olfactory epithelium. Here they terminate in slight enlargements each of which bears eight to twelve fine hairs. The central processes are very slender, and join together in the submucosa to form bundles of

the olfactory nerves. These pass back as a large number of parallel fascicles which penetrate the cribriform plate of the ethmoid bone; in the intracranial cavity they form a dense plexus of fibres over the surface of the olfactory bulb (Plate VIII, fig. 3). Here, as described by Ramón y Cajal (1911) and others, the axons of the receptive elements are interwoven in a very complicated manner; they branch only as they enter the glomeruli, where they end in synaptic relation to the dendrites of mitral cells and *cellules à panache* (which we shall term *tufted cells*).

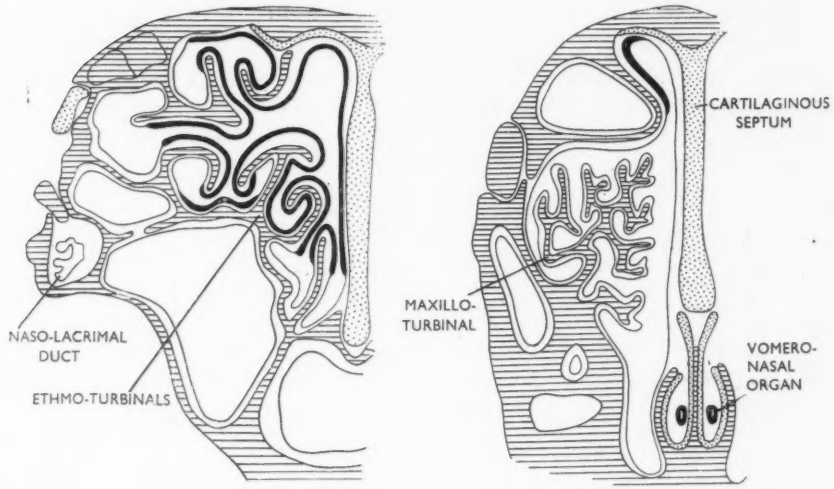
The different layers of the olfactory bulb, and the cells which they comprise, are shown in Plate I, fig. 1. The various structural details of these elements, and their relationship to one another, are complex, and for descriptions of them the reader is referred especially to Ramón y Cajal's account. The essential projections of olfactory impulses are, according to this authority, as follows: Mitral cells receive impulses directly from olfactory nerves in the glomeruli through their main or descending dendrites, and project them by means of long axons into the olfactory tract; and tufted cells, which also have dendrites both in the glomeruli and in the external plexiform layer, probably project impulses through the intrabulbar component of the anterior commissure to the opposite olfactory bulb. Collaterals of mitral cell and tufted cell axons, and synapses with short-axon cells within the bulb, provide circuits for "reinforcement" of olfactory impulses.

With details of secondary olfactory connexions we are not concerned here. These connexions have been studied recently by Le Gros Clark and Meyer (1947), who established that the olfactory tract terminates in a limited part of the piriform cortex and olfactory tubercle and in the cortico-medial group of amygdaloid nuclei, while the olfactory component of the anterior commissure ends bilaterally in the bed nucleus of the stria terminalis and central amygdaloid nucleus, and in the contralateral olfactory bulb mainly in the internal granular layer.

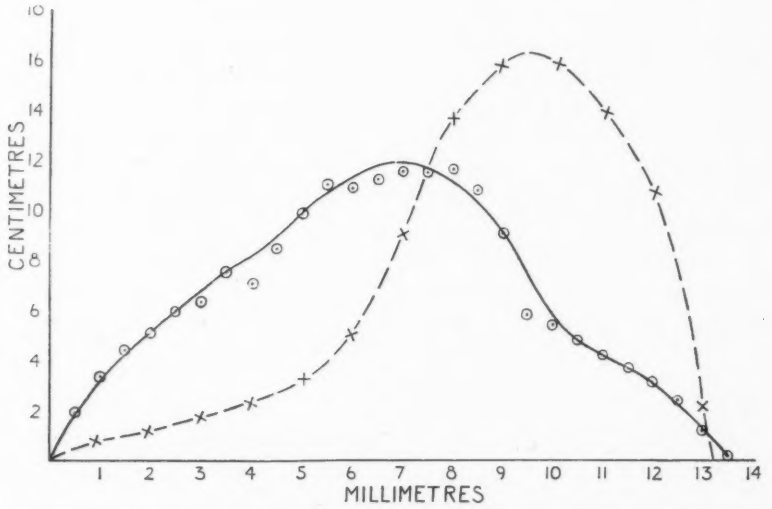
Surface Area of the Olfactory Mucous Membrane

In each of the two series of sections taken through decalcified skulls of rabbits about four months of age, the entire olfactory region is included. The olfactory epithelium has a characteristic appearance even in sections stained with hæmatoxylin and eosin, and is thus easily distinguished from the ciliated epithelium of the respiratory region of the nasal cavity (Plate VIII, fig. 2). The olfactory mucous membrane covers the postero-dorsal part of the nasal septum and the elaborately folded ethmo-turbinals (text fig. 1 A and B).

In order to obtain an estimate of the total surface area of the olfactory epithelium, representative sections at intervals of 250 μ were taken; from a



TEXT-FIG. 1.—Semi-diagrammatic transverse sections through (A) the middle and (B) the posterior third of the nasal cavity, showing the distribution of olfactory epithelium on the ethmo-turbinals (heavy line) × 5.



TEXT-FIG. 2.—Graphs constructed to show the extent of olfactory epithelium (ordinates) measured in a series of sections at ½ millimetre intervals through the rabbit skull in (A) a frontal plane (interrupted line) and (B) a sagittal plane (continuous line). In the case of the frontal sections, the ordinates are represented at two-thirds the actual dimensions.

projected image, magnified twenty times, the extent of the olfactory epithelium appearing in these sections was traced and the length of each tracing measured with thread. In transverse sections followed from the front of the nasal cavity posteriorly, the extent of olfactory epithelium seen in each section naturally increases gradually as more of the septum is covered and the ethmo-turbinals progressively expand; finally, the extent diminishes rapidly as the cribriform plate is reached. These measurements were plotted on squared paper (fig. 2), and from the graph so obtained the actual area of olfactory epithelium was measured. A similar procedure was employed with the sagittal sections (fig. 2).

The total surface area of olfactory epithelium in the first specimen was found to be 10·2 cm.², in the second 8·4 cm.². This gives an average total area of 9·3 cm.², or about 4·5 cm.² on either side.

Olfactory Receptors

Density of olfactory receptors.—In tangential sections of the olfactory mucous membrane on the nasal septum impregnated with silver, the olfactory rods are distinctly seen in cross section (Plate VIII, fig. 4). The number of olfactory rods in a given area of epithelium at known magnification was obtained in two series of preparations by projecting the image of the rods on to squared paper with the aid of an Abbé camera lucida, as described elsewhere (Allison and Chacko, 1949), and also by direct counts of rods in photomicrographs. From these figures it is easily possible to calculate the density of receptors in different parts of the olfactory epithelium on the nasal septum.

It was found that the density of receptor cells varies to some extent in different parts of the nasal septum. Random samples of epithelium from the posterior part of the septum gave counts of about 140,000 rods per mm.²; those from the middle of the olfactory epithelium on septum ranged around 115,000, and others from near the anterior extremity of the epithelium were as low as 81,000. Thus, there appears to be a tendency for the density of receptors to increase from the periphery of the olfactory epithelium inwards, and our preparations indicate that this gradient is fairly even. However, our material is perhaps too limited to allow of final conclusions on this point. The average density of receptors, taken from twenty-four different counts distributed over the entire extent of the olfactory epithelium, is approximately 120,000 per mm.². This figure is somewhat lower than that given in the preliminary statement by Le Gros Clark and Warwick (150,000), the difference being accounted for by the recognition of a gradient in the density of the receptors.

Total number of olfactory receptors.—The total number of olfactory

receptors is, of course, the product of the surface area of the olfactory epithelium in mm.^{2} (estimated above as averaging 930) and the number of rods per mm.^{2} (about 120,000), i.e. 111,600,000. Thus, it may be taken that the number of receptors in the rabbit is of the order of 100,000,000 or 50,000,000 on each side.

The number of glomeruli in the olfactory bulb.—For the purpose of this study, five series of sections (15 μ in thickness) through the olfactory bulbs of rabbits were used. In three of these series the sections were cut in a coronal plane and in two in a sagittal plane. They were stained either with protargol or Borrel's methylene blue. Material impregnated with silver was found to be the most satisfactory for the study of the glomeruli, for they are sometimes closely applied to one another and therefore may be difficult to define as separate structures in Nissl sections, even though in the latter they are as a rule circumscribed by fairly well-defined capsules of small periglomerular cells. But, in some cases, bands of granular and neuroglial cells are found within the glomeruli, appearing as septa dividing single glomeruli into small compartments, and the latter might occasionally be counted as whole glomeruli.

In well-fixed and well-impregnated olfactory bulbs, which show no signs of atrophic changes following the chronic rhinitis from which laboratory animals frequently suffer, the glomerular units appear as relatively large rounded structures forming a stratum over the surface of the bulb, and actually visible macroscopically in sections (Plate VIII, fig. 3). In a single sagittal section through the central axis of a bulb, as many as 180 of these structures may be counted. In general, they have an approximately spherical contour, or they may have a somewhat discoid shape as the result of a slight flattening in relation to the surface of the bulb. In any one section, the glomeruli appear to vary considerably in size. However, if single glomeruli are traced through the serial sections and their maximum diameters measured, it is apparent that their total diameters in a sagittal or transverse direction do not vary to any great extent. Diameter measurements were made on samples of 60 glomeruli selected at random in different parts of the bulb. These data show that the sagittal diameters have a range of 160 μ to 210 μ, with an even curve of distribution about a mean of 185 μ, while the transverse diameters have a range of 170 μ to 215 μ with a mean of 190 μ. No evidence was found that the total diameters of the glomeruli vary with their relative position in the bulb. From what has been said, it is of course clear that each individual glomerulus will appear in several successive serial sections, and the apparently smaller glomeruli seen in a single section are the result of tangential sections through the main structures.

In order to obtain a true count of glomeruli, the method devised by

Abercrombie (1946) for estimating nuclear populations from microtome sections was adapted for our purpose, since it should apply equally well to large spheres as to small: if A is the crude count of parts of glomeruli in all sections, M is the thickness in μ of each section and L the average diameter in μ of a glomerulus, then the true glomerular count N is given by the formula $N = A \frac{M}{L+M}$. Generally speaking, the number of glomeruli appearing in successive serial sections is reasonably constant, so that parts of glomeruli were counted in every sixth section, and the number in intervening sections assumed. The average diameter, 185 μ (taken from measurements in transverse sections), was applied to the calculation of glomerular number from sagittal sections, and the average diameter, 190 μ (from sagittal sections), applied to the count from transverse sections.

The glomerular counts thus obtained in five different bulbs were 1,859, 1,852, 1,912, 1,981 and 1,312. The latter count, however, is suspect because of apparent partial atrophy of the bulb, so that the mean count, 1,901, was taken from the four remaining figures. We conclude, then, that there are approximately 1,900 glomeruli in each olfactory bulb of rabbits.

The number of mitral cells and tufted cells (Ramón y Cajal's cellules à panache) *in the olfactory bulb*

Direct counts of mitral cells were made from every sixth section of four series of 15 μ sections through the olfactory bulb, stained with Borrel's methylene blue. Only those cells with distinct nucleoli or plasmosomes were counted (occasional cells having two plasmosomes, usually both in the same section): according to Jones (1937) it is unnecessary to make a correction for split nucleoli in counts of nerve cells in sections 10 μ or more in thickness. The two types of large cell in the olfactory bulb are recognized without difficulty (Plate VIII, fig. 1). Mitral cells lie for the most part in a single layer: they are massive and have many coarse Nissl bodies. Tufted cells have also a deeply basophilic cytoplasm; they are of medium size and irregular shape, and the majority are found towards the outside of the external plexiform layer, some reaching as far as the layer of glomeruli where they lie among the small periglomerular cells. The counts of mitral cells obtained in the four bulbs were 45,406, 47,368, 48,824 and 43,040. The mean of these figures is 45,159.

It should be noted that amongst the large neurons in the layer of mitral cells are a few smaller neurons to which Cajal refers as "petites cellules mitrales." They are, in fact, probably tufted cells, but because there are no absolute criteria for recognition of the two cell-types, they have been here included in the count of mitral cells. The figure given is thus somewhat too high for the typical, very large, mitral cells. There are not many displaced mitral cells (*cellules mitrales déplacées*) inside the mitral cell

layer in the olfactory bulb of the rabbit. It may be concluded on the basis of these observations that there are approximately 45,000 mitral cells in each olfactory bulb of rabbits.

It was found in preliminary counts that the number of tufted cells bears a fairly constant relation to the number of mitral cells, there being about 2·5 times as many tufted cells as mitral cells in sections of the olfactory bulb cut in either transverse or sagittal planes. Thus, it is estimated that the number of tufted cells in each olfactory bulb is of the order of 130,000.

The number of fibres in the olfactory tract.—The fibres in the olfactory tract were counted in four series of transverse sections impregnated with protargol. In these sections, taken just behind the accessory bulb, the olfactory tract appears on the surface of the brain as a compact band of regularly arranged fibres, the great majority of which are cut transversely (Plate VIII, fig. 5). In each case, in twelve random samples from different parts of the olfactory tract the number of fibres per unit area was obtained, using a camera lucida as before: the density appears to be fairly uniform. The area of the tract (as found by projection) was then multiplied by the average density of axons in order to ascertain the total number of fibres in the tract.

The counts obtained on four specimens were 59,877, 56,481, 62,886 and 65,073, the mean of which is 61,079. It may be concluded, therefore, that each olfactory tract in the rabbit's brain at the point where it emerges from the bulb, contains about 60,000 fibres.

Discussion

The numerical relationship of the primary olfactory neurons to glomeruli and to secondary olfactory neurons: It was established by early investigators that the incoming olfactory nerves terminate in the glomeruli, where their varicose arborizations lie in close apposition to the dendrites of mitral cells and tufted cells. Glomeruli are well circumscribed, so that they appear to act to some extent as independent functional, as well as anatomical, units. Further, each mitral cell and tufted cell has (according to Van Gehuchten and Martin, 1891), in addition to a number of accessory dendrites in the external plexiform layer, only one main or descending dendrite, and the latter branches freely in a single glomerulus. If this is so, each glomerular system (if it may be so termed), while connected with other systems by short-axon granular cells and collaterals of mitral cells and tufted cells, receives impulses from a segregated and independent group of olfactory fibres and projects impulses through a limited number of mitral and tufted cells to the secondary olfactory centres at the base of the telencephalon.

Le Gros Clark and Warwick (1946), basing their observations on the

septal mucosa, found that after small lesions in the olfactory bulb the retrograde atrophy of receptors is not confined to any one region of the olfactory epithelium, but appears as a partial degeneration over the whole septum. This observation suggests that there is nothing like a point-to-point localization of the projection of the olfactory epithelium on to the olfactory bulb, but rather a projection which is so diffuse that a small part of the epithelium may be represented to some extent over a considerable area on the bulb. It follows that each glomerulus probably receives fibres from receptors which are widely dispersed through the olfactory mucous membrane (and possibly subserving the same type of olfactory sensation).

In the present study we have estimated that in rabbits there are on each side approximately 50,000,000 olfactory receptors, and in each olfactory bulb about 1,900 glomeruli, 45,000 mitral cells and 130,000 tufted cells. Hence, in each glomerulus impulses from something of the order of 26,000 receptors are received and relayed through 24 mitral cells and 68 tufted cells. The glomerulus is thus clearly an admirable structure for effecting spatial summation, and this is, presumably, the basis for the high acuity of the sense of smell. The anatomical distinction between glomerular systems suggests that they may play, severally and in combination, an important part as a central mechanism for olfactory discrimination, but there is at present no physiological evidence on this point.

The contribution made by different cell-types in the olfactory bulb to the olfactory tract. The most comprehensive analyses of the finer structure of the olfactory bulb have been made mainly with the Golgi technique. While the general relationships of the different cell-types in this organ are well established, there has been some divergence of opinion on a number of points, in particular, which cells in the bulb contribute their axons to the olfactory tract. It is agreed by most authorities that the axons of mitral cells reach the tract, and Van Gehuchten and Martin (1891) stated that axons of tufted cells (*cellules empanachées*) have a similar trajectory ("Toutes les cellules nerveuses situées dans la couche moyenne du bulbe se comportent donc de la même facon, quels que soient leur forme, leur position ou leur volume . . ."). Cajal (1911), however, denied this: while admitting that the axons of tufted cells are fine and extremely difficult to follow through the maze of connexions in the internal plexiform layer, he maintained that they pass into the anterior limb of the anterior commissure.

The question was reopened by Winkler (1918), who reported a number of experiments in which he sought retrograde degeneration in the olfactory bulb after lesions involving the olfactory tract. When the tract is severed in young rabbits and the olfactory bulb on the same side is examined

some months later, it is found that mitral cells are decreased in size, presenting "different stages of total or partial pyknomorphy"; but this change is, Winkler pointed out, not as marked as would be anticipated in cells with their axons cut. Because he believed with Van Gehuchten and Martin that the tufted cells have a projection into the olfactory tract, Winkler was surprised to find these cells unchanged after the operation. Unable to explain the apparent discrepancy between his own experimental results and the Golgi studies of previous investigators, Winkler proposed that the olfactory tract "originates from a fibrillar reticulum intercalated between mitral cells and its fibres," which he compared with the terminal reticulum in the deep part of the molecular layer of the piriform cortex where the tract ends.

It is now generally recognized that cells in different parts of the central nervous system may react in several ways to section of their axons. In most instances axonal destruction is followed by complete degeneration and disappearance of the cell body: but in other cases (for example, in the medial geniculate nucleus after hemi-decortication) the cell survives for a considerable time, often in a partially atrophic condition. Thus, absence of more severe changes in mitral cells after severance of the olfactory tract cannot alone be adduced as evidence that these cells do not contribute fibres to the tract, especially if it is taken into consideration that mitral cells have well-developed collaterals within the olfactory bulb which may remain in a functional state even after the axon is destroyed. Indeed, all available evidence supports the view that the olfactory fibres do in fact arise, at least in part, from mitral cells.

Whether tufted cells also contribute their axons to the olfactory tract is still an open question. The results of the present investigation throw some light upon this matter. We have found that there are, on an average, a little more than 45,000 mitral cells in each olfactory bulb in rabbits, while in the olfactory tract there are about 60,000 fibres. The latter figure is somewhat too high if only axons arising in the main olfactory bulb are considered, because it must include fibres from the accessory bulb and also some of the fine collaterals which are known to terminate in the nearby anterior extremity of the area prepiriformis. If these factors are taken into consideration it is likely that there is an approximately 1 : 1 relationship between mitral cells and the axons in the olfactory tract which have their origin in the main bulb. Thus it seems reasonable to conclude that (so far as the main bulb is concerned) the tract is formed for the most part, if not entirely, by a projection of mitral cells, and that most, if not all, of the tufted cell axons go elsewhere, probably, as Cajal affirms, into the anterior commissure. If this is the case, tufted

cells should remain unchanged after transection of the olfactory tract, which is just what Winkler found.

Summary

(1) The total surface area of olfactory mucous membrane in the nasal cavity of each side in rabbits 4 months of age is about 4·5 cm.^{2}.

(2) There are on an average 120,000 olfactory receptors per mm.^{2} of epithelium. The total number of receptors is, therefore, of the order of 50,000,000 in the nasal cavity of each side.

(3) In each olfactory bulb there are about 1,900 glomeruli, 45,000 mitral cells and 130,000 tufted cells (*cellules à panache*). Thus each glomerulus receives impulses from something like 26,000 receptors and relays them through 24 mitral cells and 68 tufted cells.

(4) The number of fibres in each olfactory tract is approximately 60,000. It is concluded that at least the majority of these arise from mitral cells, and that most, if not all, tufted cells have their central projections in the anterior limb of the anterior commissure.

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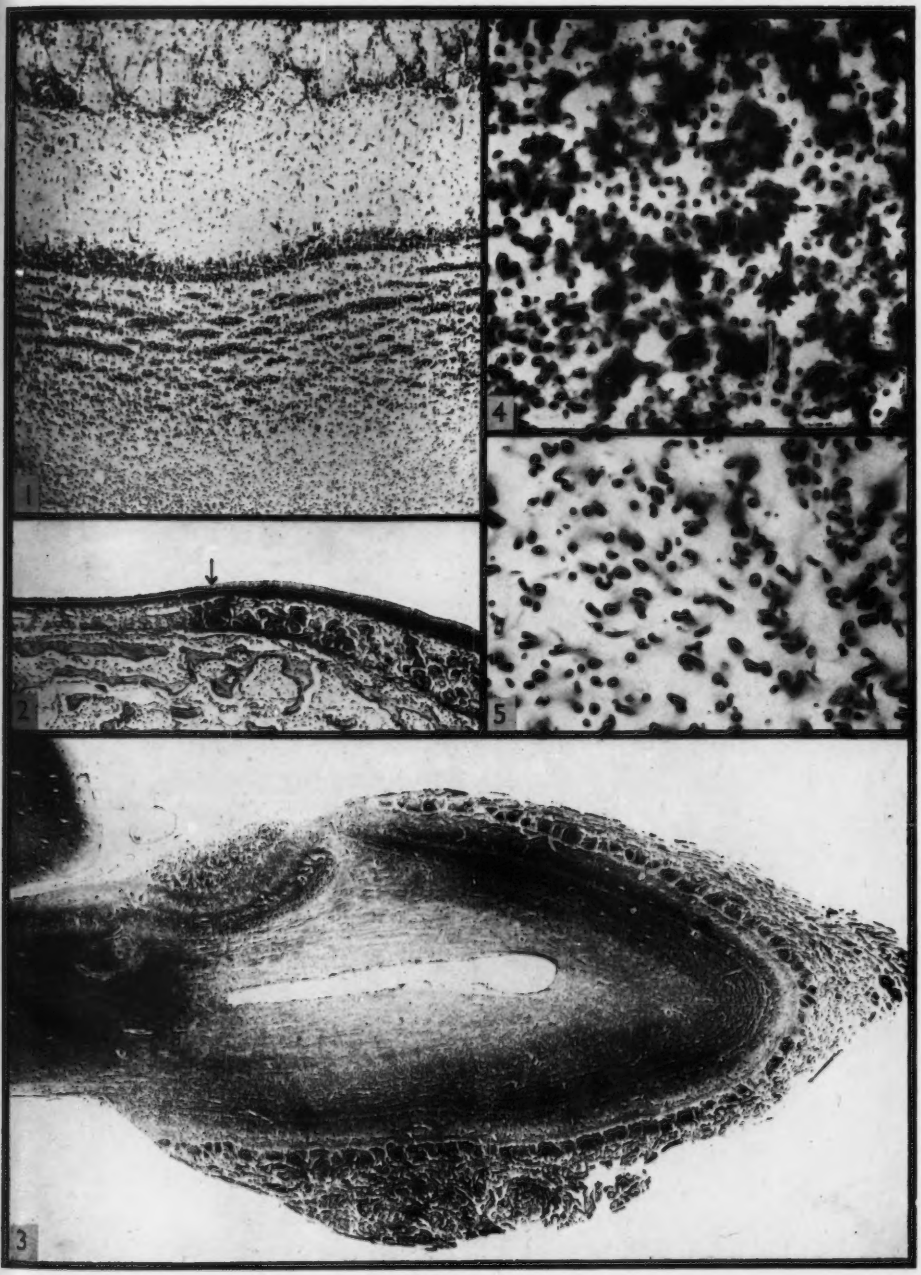
PLATE VIII.



To illustrate article by A. C. Allison and R. T. Turner Warwick. Legends overleaf.

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EXPLANATION OF PLATE VIII

All illustrations are unretouched photomicrographs of material prepared from young rabbits.

FIG. 1.—Frontal section through the outer layers of the olfactory bulb. Nissl stain, × 80. From above downwards are seen the glomerular layer, the external plexiform layer, the layer of mitral cells, and the layer of granule cells.

FIG. 2.—Frontal section through an ethmo-turbinal process, showing with an arrow the abrupt junction between olfactory (right) and respiratory epithelium. Hæmatoxylin and eosin, × 75.

FIG. 3.—Sagittal section through the middle of the olfactory bulb. Protargol × 20. On the surface of the bulb is seen the intricate plexus formed by the olfactory nerve fibres. Deep to this is a single layer of glomeruli. Deep to this, again, are the external plexiform and granular layers, and in the centre of the bulb the olfactory ventricle is seen. Above and to the left is the accessory bulb; note the absence of glomerular units in this structure.

FIG. 4.—Tangential section of the olfactory mucuous membrane, showing the olfactory "rods" in cross section. Protargol, × 900.

FIG. 5.—Transverse section through the lateral olfactory tract, showing the arrangement and distribution of its individual fibres, × 1,100.

EXPERIMENTAL "ALLERGIC" ENCEPHALOMYELITIS

BY

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INTRODUCTION

BRAIN tissue from many mammalian species contains some non-infective chemical agent which is specifically pathogenic to the mammalian nervous system.

The first examples of this phenomenon were provided by the neuroparalytic "accidents" of anti-rabic treatment; for the earlier views that such accidents were due to infection with the "virus fixe" of the vaccine were scarcely tenable when it was found by numerous independent workers at different times that sterile "neurovaccines" prepared from uninfected animals were equally liable to result in paralysis. This earlier work has been adequately summarized by Hurst (1932).

But the specific neurotropic effect of sterile brain extracts injected subcutaneously and intramuscularly into animals (usually rabbits) was capricious and infrequent in all the earlier experimental studies and was either not investigated at all or not substantiated by histological examination. Also, such positive results as were reported were apt to be discounted in the light of McCartney's demonstration (1924) of the naturally-occurring (encephalitozoal) encephalitis of rabbits.

Rivers and Schwentker (1935) and Ferraro and Jervis (1940) observed encephalomyelitic lesions in monkeys following a prolonged period (up to 405 days) of injections of rabbit brain extracts but the number of experimental animals was small, 8 and 7 respectively. Also, the monkey is naturally prone to encephalitis and even to demyelinating disease (Levaditi, Lépine and Schoen, 1930; Schob, 1931; Scherer, 1932).

Some twenty years ago, workers investigating local hypersensitization in tuberculosis noticed that antibody formation to substances such as egg-white and horse serum was often considerably higher in tuberculous than in non-tuberculous guinea-pigs. Dienes (1928) was able to produce an enhanced antibody formation to these proteins by using *dead* tubercle bacilli. This enhancing, or *adjuvant*, effect of dead tubercle bacilli in antibody formation to other proteins was investigated further by Freund and McDermott (1942) and by Freund and Bonanto (1944) who showed that the addition of sterile lanoline and liquid paraffin enhanced the reaction even more.

In 1928, Witebsky and Steinfeld had produced some serological evi-

dence that injections of *brain* substance can elicit a specific antibody. Arising from this observation Kopeloff and Kopeloff in 1944 showed, by complement-fixation methods, that antibodies were produced in the monkey following the injections of sterile brain tissue from sheep; but this result occurred with regularity only when the "adjuvant" technique was employed.

These two lines of research converged in the experiments of Kabat, Wolf and Bezer, and of Morgan, who reported, independently, in 1947 that disseminated encephalomyelitis could be regularly and rapidly produced in Rhesus monkeys by a few subcutaneous or intramuscular injections only of a sterile injection mass of brain tissue administered in a base of lanoline and liquid paraffin containing heat-killed tubercle bacilli. In the experiment of Kabat, Wolf and Bezer, of 10 monkeys injected with adult monkey brain plus "adjuvants," 9 developed lesions in the central nervous system: of 9 given adult rabbit brain with "adjuvants," 8 developed disseminated encephalomyelitis; "adjuvants" plus fœtal rabbit brain gave negative results in all of 7 monkeys, and "adjuvants" plus rabbit-lung likewise gave negative results in the 4 animals used. In the experiment of Morgan, homologous tissue only (i.e. from Rhesus monkeys) was used for injection into the test monkeys: 8 out of 12 treated with spinal cord and "adjuvants" developed disseminated encephalomyelitis, and of 10 treated with "white matter" from monkey brain with "adjuvants," 4 developed encephalomyelitis. She claimed, however, that cerebral "grey matter" with "adjuvants" failed to produce lesions in 10 monkeys; and likewise peripheral nerve, kidney (both along with "adjuvants"), and "adjuvants" alone produced no lesions.

The present paper reports a series of experiments on these problems which I have carried out during the past three years. As a preliminary, certain data, relevant to the later discussion, are reported from some "negative" experiments in which "adjuvants" were not employed. But the majority of the experimental data concerns experiments in which the "adjuvant" technique was used. In these latter experiments, use has been made of over 300 guinea-pigs, 150 rats and 12 rabbits as test animals (excluding those sacrificed to provide tissue for the various test emulsions).

Since this work has been in progress, a number of further papers have appeared on this subject.

Most notably, Kabat, Wolf and Bezer (1948) report that "the factor in brain tissue which induces acute disseminated encephalomyelitis, when injected into Rhesus monkeys as an emulsion with adjuvants, has been found in human, monkey, rabbit and chicken brain, but is absent from frog and fish brain." They say, also, that this factor was unaffected by formalin treatment, by boiling, and by exposure to ultrasound; but, "after

extraction of brain tissue with alcohol or with acetone neither the extract nor the extracted residues showed any capacity to induce encephalomyelitis except for very mild lesions without symptoms discovered on pathological examination in one animal injected with the acetone residue" (three animals only, however, appear to have been tested in each of these series).

Ferraro and Cazullo (1948) have sought to follow the evolution of this experimental encephalomyelitis (ECM) in a more "chronic form" (three months after the onset of symptoms) which they succeeded in producing in a few monkeys by reducing considerably the dosage of the brain substance and of the killed tubercle bacilli. Their findings of "patchy sclerosis" in two animals will be discussed later.

The production of a similar experimental "allergic" ECM in *rabbits* has been reported by Morrison (1947). Of his 21 rabbits, 3 were given repeated injections (95 to 104) over a period ranging from 348 to 390 days with saline suspension of rabbit cord—with negative results; 3 were treated with rabbit cord suspension in which lecithin had been hydrolysed by lecithinase (*Cl. welchii* filtrate) and the lecithinase then removed—with 2 positive results. Of 5 treated with a preparation identical with the preceding except that the lecithinase was retained, there were 3 positives. Of the 10 treated with brain tissue along with "adjuvants," no less than 9 developed encephalomyelitis. The interesting feature in Morrison's instance, was the presence of *histological* changes in the brains of his rabbits—in contrast to the experience of Weston Hurst (1932) (who, however, was not employing the "adjuvant" technique), and to my own failure to find histological lesions in the rabbit brains in the present work (though, in my case, guinea-pig brain emulsion in "adjuvants" was employed against rabbits).

Finally, since the present work had been well under way, two teams of workers—Freund, Stern and Pisani (1947) and Jervis and Koprowsky (1948)—have actually reported the production of this lesion in *guinea-pigs*, in both instances, however, following *single* injections only of their respective injection emulsions (in the former case, of homologous brain tissue; in the latter case, of heterologous—rabbit—brain). Incidentally, it may be noted here that Freund and his colleagues found killed *M. butyricum* equally efficacious with *M. tuberculosis* as an "adjuvant." Freund, Stern and Pisani reported no less than 16 animals out of the 19 used with neurological sequelæ but it is notable that only 10 died or were killed because of paralysis. Jervis and Koprowsky reported that 24 out of the 30 animals used developed clinical manifestations fourteen to eighteen days after the injection; 7 progressing to death, 5 with temporary remission but final complete paralysis, while 12 recovered. It will be evident, therefore, that the incidence of "positives"—by the criteria to which I have restricted the

diagnosis of "positive" in my own experiments (i.e. combining progressive and gross clinical paralysis with frank histological lesions)—in the experiments of both of these teams of workers was, respectively, 10 out of 19 and 12 out of 30. In the present experiments it will be seen that this incidence was 51 out of 91. There is, then, in all such experiments, a remarkable constancy of incidence to which attention is again drawn in the discussion.

Section A

Preliminary Experiments without "Adjuvants"

(*a*) *Rats:*

(1) Experiment α: *Effect of intraperitoneal injections of a sterile emulsion of rabbit brain.*

The emulsion was a 20 per cent w/v sterile rabbit brain in physiological saline. Dose: 1 ml. daily for five days.

These rats remained symptom-free and were sacrificed on the 30th day. No histological lesions were detected in the CNS, kidneys, liver or lungs.

(2) Experiment β: *Attempt to reproduce cerebral Arthus phenomenon in rats, with horse serum.*

Six rats received an initial dose of 1 ml. of normal horse serum intraperitoneally and eighteen days later a second dose of 1 ml. also intraperitoneally. No anaphylactic responses appeared. Another 6 rats received 1 ml. daily for five days. A third group of 6 received 1 ml. intraperitoneally, and twelve days later an intracerebral dose of 0·2 ml. which they survived. The animals in all three groups were killed. Histological examination of the brains in third group showed traumatic lesions only but no detectable Arthus reaction. The livers, spleens, and kidneys, as well as the CNS in all three groups were histologically examined: no lesions were found.

(3) Experiment γ: *Attempts to produce an antiserum to rat brain.*

Two young female Dutch rabbits were given 1 ml. doses of a sterile emulsion of normal rat brain (10 per cent w/v in saline with 0·25 per cent phenol as preservative) subcutaneously on the 1st, 3rd, 5th and 7th days of the experiment. On the 10th day, 5 ml. of the same emulsion were given intraperitoneally. No clinical reactions were observed in these rabbits which were bled on the 16th day, approximately 35 ml. of blood (taken from the ear with a modified Sjövall's suction apparatus) being collected each time from each animal. The serum was separated from the clot and 5 ml. of this serum was injected intraperitoneally into each of 6 rats. No clinical reactions were observed in these rats. On the 30th day, the "immunized" rabbits were again bled as before and their pooled sera again injected in 5 ml. doses into the same rats. Two also received 0·2 ml. each intracerebrally. No reactions were observed in any of the rats. These were sacrificed fifty-four hours later. No histological lesions were detected in the brain, liver, lungs or kidneys of any of them.

(4) Experiment δ: *Attempts to produce cerebral lesions in rats by prolonged courses of subcutaneous injections of aqueous and alcoholic extracts prepared from human brain according to the method of Rivers and Schwentker* (1935).

As test animals, 50 rats were used, half receiving aqueous extract and half, alcoholic extract. Daily subcutaneous injections were given (except Sundays) for fifty days—i.e. 43 injections. At this stage, 4 from each group were sacrificed for histology.

Then beyond this point, a variation was introduced into the experiment as compared with that of Rivers and Schwentker—viz. the animals in each of the two series were now subdivided into three subgroups each. One subgroup in

each series continued to receive daily subcutaneous injections (0·5 ml.) of the appropriate extract; the second subgroup in each series was allowed a three-week rest period (to see whether sensitization could occur) and then given a further single injection of 1 ml. of the appropriate extract; the third subgroups received 0·5 ml. of extract plus 1 ml. of horse serum daily for ten days and then sacrificed. No clinical reactions were observed in any group. The whole 50, when finally sacrificed, were examined histologically in respect of the CNS, and in 2 or 3 from each subgroup the livers, spleens, kidneys and lungs were also examined histologically. No histological lesions were detected.

As a variant of this experiment, a further 10 rats received a "short, massive course" of injections of these two extracts—5 ml. intraperitoneally every day for five days. No reactions were observed. Two from each group were sacrificed on the 7th day and the remainder on the 16th day from the first injections. Histologically, all were free of brain and other visceral lesions.

(5) Experiment ϵ: *Investigation of the effects, in rats, of injections of rat brain tissue combined with killed betastreptococci.*

This was an attempt to apply to brain the technique used by Cavelti and Cavelti in their alleged production of "progressive glomerulonephritis." 20 test rats were used (throughout this work the rats used were from a hooded strain emanating originally from the Lister Institute and maintained for several years at the Rowett Institute, Aberdeen). The results were entirely negative; furthermore, no renal lesions were detected microscopically in any of these animals.

(*b*) *Guinea-pigs:*

Experiment ς: This was a repetition of Experiment β, using guinea-pigs (12) instead of rats. No lesions were produced in any of the viscera except in the case of the brain in 4 out of 6 which received the sensitizing dose of horse serum intracerebrally. These 4 showed marked hæmorrhage (occasionally with thrombosis), an intense meningoencephalitic reaction of polymorphonuclear neutrophil and (notably) eosinophil leucocytes, œdema and myelin pallor, and gitter cell reaction. This reaction extended well beyond the actual needle track.

This production of the "Arthus" reaction in the brain of the guinea-pig confirms the findings of Alexander and Campbell (1937).

Section B

Experiments with "Adjuvants"

Preliminary note on technique.—This has been standardized throughout all the experiments described below.

(*a*) Animals: All brains used for the injection emulsions have been taken from the same stock as the test animals to be injected. All animals have been subjected to a routine quarantine for six to eight weeks to exclude, or at least to minimize, fallacies from intercurrent disease. All animals selected for use were three-quarter grown at the beginning of the various experiments; all were thriving and none had to be rejected during the quarantine period.

Diet has been a standard one consisting of 66 per cent scalded sugar beet pulp and 33 per cent crushed oats with liberal supplies of greens and of straw.

Animals to be used for the preparation of injection emulsions were sacrificed by exsanguination. The heads and necks were allowed to soak in 70 per cent alcohol for thirty minutes; then with sterile instruments they were opened and the brains removed into a sterile weighed beaker.

The test animals for injection in the individual experiments were housed in common pens. A system of pen rotation was employed every week so that the risk of any intercurrent disease that might have appeared (or the disseminated encephalomyelitis itself, were it possible that this were a spontaneous infection exacerbated by the injections) would be equally shared by all series alike.

(*b*) Injection emulsions: The brains for each emulsion were pooled, weighed in the sterile beaker, given a preliminary rough grinding in a glass mortar without sand, then washed with measured saline (containing 1 per cent phenol as a preservative) into a Waring blender. Sterile liquid paraffin (B.P.) containing 125 mg. of heat-killed *M. tuberculosis* per 100 ml. of paraffin was added. Then the melted lanoline base—at about 65° C.—was added slowly to this mixture in the blender. The whole was allowed to mix for periods of three minutes at a time (to avoid overheating) until the mixture was completely homogeneous. This final emulsion is almost perfectly white, and though viscous can be injected quite readily (especially if warmed to 37° C.) through a large serum needle (Solila 19).

In the tables illustrating the various experiments, the constitution of the emulsions has been expressed simply, for ready comparison, in 100 ml. quantities.

In the first experiment, the emulsions were allowed to stand for two hours only after preparation and then heated to 60° C. for an hour "to inactivate autolytic enzymes." In the later experiments it has seemed that a slightly more potent emulsion can be obtained by increasing the time for autolysis to four or five hours.

All emulsions have been repeatedly tested for sterility before and during the period of their use. None has shown any bacterial contamination at any time.

EXPERIMENT I.—*To test the visceral effects, in guinea-pigs and rats, of repeated subcutaneous injections of sterile guinea-pig and rat-brain emulsions with "adjuvants."*

36 guinea-pigs and 36 rats were injected at weekly intervals, with intermissions every 4th week. The constitution of the injection emulsions is shown in Table I.

TABLE I.—COMPOSITION OF INJECTION EMULSIONS IN EXPERIMENT I

Emulsion "KP"		*Emulsion "MP"*	
Guinea-pig brain	8·0 grm.	Guinea-pig brain	8·2 grm.
Physiol. saline with 1 per cent phenol ("phenol-saline")	25·0 ml.	Phenol saline	25·0 ml.
Aquaphor	25.0 ml.	Falba	25·0 ml.
Liquid paraffin	50·0 ml.	Liquid paraffin	50·0 ml.
M. tuberculosis (heat-killed)	0·0625 grm.	*M. tuberculosis* (heat-killed)	0·0625 grm.
Emulsion "KR"		*Emulsion "MR"*	
Rat brain	7·9 grm.	Rat brain	8·3 grm.
Phenol-saline	25·0 ml.	Phenol saline	25·0 ml.
Aquaphor	25·0 ml.	Falba	25·0 ml.
Liquid paraffin	50·0 ml.	Liquid paraffin	50·0 ml.
M. tuberculosis (heat-killed)	0·0625 grm.	*M. tuberculosis* (heat-killed)	0·0625 grm.

It will be seen that the constitutions of the two guinea-pig brain emulsions were identical except for the proprietary lanoline base, "aquaphor" being that used by Kabat, and "falba" being that used by Morgan. 24 guinea-pigs received homologous brain emulsion; and 12, the rat-brain emulsion. The 36 rats received only rat-brain emulsions (18 "KR," and 18 "MR").

Five out of each group of 12 guinea-pigs injected with one or other of the two guinea-pig brain emulsions developed severe paralysis of upper motor neurone type (with spasticity, clonus, etc.), mostly between the 28th and 32nd days (*see* Table III). None of the other animals showed any signs of illness apart from some loss of weight during the 2nd to the 4th weeks. But those which developed paralysis did so rather suddenly and progressed to complete paralysis in three to four days, with rectal and bladder incontinence of overflow type ending, in two instances where the animals were allowed to survive long enough, in acute pyelonephritis. To

ensure uncomplicated pathology and standard histological conditions, however, most of the paralysed animals were sacrificed at the same stage—when the hind-quarter paralysis had just become complete. Autopsies were performed in all these "positive" animals and histological examination made in all organs. Microscopically, all these cases showed the same features, namely, *disseminated perivenular encephalomyelitis.*

Further clinical data on this lesion will be found in Section D below.

An interesting observation made at this time, and confirmed in the later experiments, was that, apart from the "positives," in each series receiving guinea-pig-brain emulsion, 2 animals (and a doubtful third) showed a transient paresis; but further weekly injections, for fourteen weeks, of these as of the other "negative" animals, failed to provoke any further symptoms.

The 12 guinea-pigs receiving "adjuvants" along with rat brain remained completely well and were observed up to 321 days when they were finally sacrificed (*see* Experiment III). Histologically, they showed no trace of any encephalomyelitis, nor, indeed, any residual gliosis or other appreciable lesion; other viscera were likewise negative.

In the rat series (in the present experiment injected only with rat-brain emulsion; but *see also* Experiment IV) none of the 36 animals developed and neurological symptoms and all were likewise negative histologically when sacrificed over 300 days after the commencement of the course of injections.

This "pilot" experiment indicated briefly, then, that subcutaneous injections of homologous brain tissue with "adjuvants" was capable of producing encephalomyelitis in guinea-pigs, but apparently not in rats; and that the nature of the proprietary lanoline base, whether "falba" or "aquaphor," was unimportant. In contrast to guinea-pig brain, rat brain injected subcutaneously into guinea-pigs failed to produce any cerebral (or indeed any other visceral) lesions.

EXPERIMENT II.—*To confirm the production of specifically cerebral lesions in guinea-pigs by the repeated subcutaneous injections of sterile homologous brain tissue with "adjuvants"; to test the effects of similar injections of sterile emulsions of comparable concentrations prepared from peripheral nerves, from liver, from kidney and from skeletal muscle, of guinea-pigs.*

This was carried out five months after the first experiment.

The injection emulsions from liver, kidney, and skeletal muscle (thigh muscles after removal of sciatic nerves) were prepared exactly like the brain emulsions in this and in the preceding experiment, strict aseptic technique being employed throughout. Care was taken to obtain approximately the same weight of tissue for each of the emulsions (i.e. 7·5 per cent w/v for the brain emulsions and—as good measure—10 per cent w/v for the other visceral emulsions). The preparation of a peripheral nerve emulsion of comparable concentration necessitated the tedious aseptic dissection of the brachial plexuses and their main branches and the sciatic nerves from both sides. No fewer than 23 animals were needed to obtain the 6·6 grammes of tissue used. In this case the nerves were sliced up with sterile scissors into small segments roughly 2 mm. long, as a preliminary to being introduced into the Waring blender.

The final concentration of the emulsions "B," "N," "K," "L," and "M," to be injected into the five series of guinea-pigs of similar designation, are shown in Table II. In addition, in this experiment, a purely control emulsion of "adjuvants" plus saline was also used ("C"). The lanoline base throughout this experiment consisted of equal parts of falba and aquaphor; the liquid paraffin contained 125 mg. per 100 ml. of heat-killed *M. tuberculosis* as before.

The number of guinea-pigs injected with these six emulsions is shown in the bottom line of Table II. The doses were 1 ml. subcutaneously into the abdominal wall given at weekly intervals for ten weeks, with, in the present experiment, no intermission on the fourth week such as was employed in the first experiment.

TABLE II.—COMPOSITION OF EMULSIONS USED IN EXPERIMENT II
(expressed in 100 ml. quantities)

Constituents		B	N	K	L	M	C
Brain tissue ..	(grammes)	7·5	—	—	—	—	—
Peripheral nerve ..	,,	—	6·6	—	—	—	—
Kidney	,,	—	—	10·0	—	—	—
Liver..	,,	—	—	—	10·0	—	—
Muscle	,,	—	—	—	—	10·0	—
Phenol saline ..		25 ml.	25 ml.	25 ml.	25 ml.	25 ml.	25 ml.
Lanoline base ..		25 ml.	25 ml.	25 ml.	25 ml.	25 ml.	25 ml.
Liquid paraffin with heat-killed tubercle bacilli		50 ml.	50 ml.	50 ml.	50 ml.	50 ml.	50 ml.
Number of guinea-pigs		18	12	12	12	12	18

Findings: Out of the first group of 18—the brain-emulsion series—13 developed progressive paralysis, on the days shown in Table III, *and likewise 5 out of* 12 *injected with peripheral nerve emulsion.* When hindquarter paralysis was complete, the animals were sacrificed by exsanguination. Histological examination showed in all of them identical disseminated encephalomyelitis lesions; but livers, spleens, kidneys (R. and L.), adrenals (R. and L.), lungs, testes in males, muscles (hamstrings), and the sciatic nerves were examined in all instances with negative results.

TABLE III.—RESULTS IN EXPERIMENTS I AND II

KP 1	positive	5	days	after	2nd	injection	.. ..	i.e. in	12	days
KP 2	do.	6	do.		4th	do.	.. ..		29	do.
KP 3	do	11	do.		4th	do.	.. ..		34	do.
KP 4	do.	2	do.		5th	do.	.. ..		36	do.
KP 5	do.	8	do.		5th	do.	.. ..		42	do.
MP 1	positive	5	days	after	4th	injection	.. ..	i.e. in	28	days
MP 2	do.	6	do.		4th	do.	.. ..		29	do.
MP 3	do.	8	do.		4th	do.	.. ..		31	do.
MP 4	do.	8	do.		4th	do.	.. ..		31	do.
MP 5	do.	7	do.		7th	do.	.. ..		64	do.
B 1	positive	7	days	after	3rd	injection	.. ..		20	days
B 2	do.	1	do.		4th	do.	.. ..		21	do.
B 3	do.	2	do.		4th	do.	.. ..		22	do.
B 4	do.	3	do.		4th	do.	.. ..		23	do.
B 5	do.	4	do.		4th	do.	.. ..		24	do.
B 6	do.	7	do.		4th	do.	.. ..		27	do.
B 7	do.	7	do.		4th	do.	.. ..		27	do.
B 8	do.	3	do.		5th	do.	.. ..		30	do.
B 9	do.	3	do.		5th	do.	.. ..		30	do.
B 10	do.	4	do.		5th	do.	.. ..		31	do.
B 11	do.	5	do.		5th	do.	.. ..		32	do.
B 12	do.	7	do.		5th	do.	.. ..		34	do.
B 13	do.	3	do.		6th	do.	.. ..		37	do.
N 2	positive	1	day	after	4th	injection	.. ..	i.e. in	21	days
N 3	do.	4	days	after	4th	do.	.. ..		24	do.
N 4	do.	5	do.		4th	do.	.. ..		25	do.
N 5	do.	6	do.		4th	do.	.. ..		26	do.
N 6	do.	6	do.		6th	do.	.. ..		40	do.

The five survivors from the brain emulsion series continued to receive weekly injections in the same dosage as before until the 63rd day (ten injections of 1 ml. each) and were still well on the 140th day when re-employed for Experiment III.

None from any of the other series ("K," "L," "M," and "C") developed any lesions. Half of each of these series were sacrificed on the 30th day—day of maximum incidence of encephalomyelitis lesions in this work—and the other halves on the 60th day. Histological examinations from all of these were consistently negative.

Transmissibility tests on 5 of the "B" group and one of the "N" series were negative. These are referred to in Section C.

EXPERIMENT III.—*To ascertain the duration of encephalitogenic activity of sterile emulsions of brain with "adjuvants"; and to investigate whether or not guinea-pigs may be, or may become, immune to this form of experimental "allergic" encephalomyelitis.*

Three series of guinea-pigs were treated as follows:—

(*a*) Twenty-four previously untreated animals ("W" series) were injected with weekly 1 ml. doses of "old" emulsion, description of which is given below.

(*b*) Twenty-six previously treated animals—the survivors of the "KP," "MP," "B" and "N" groups from Experiments I and II—were injected with weekly 1 ml. doses of a fresh guinea-pig brain emulsion with "adjuvants."

(*c*) Twenty-five previously untreated guinea-pigs ("AO" series) were likewise injected with weekly 1 ml. doses of this fresh emulsion used in (*b*)—i.e. as controls for the potency of the emulsion.

The "old" brain emulsion consisted of some 350 ml. of the emulsion used in Experiment II, laid aside for this purpose and stored in the refrigerator at 4° C. for twenty weeks preceding the commencement of the present experiment. The "new" brain emulsion was prepared from fresh animals exactly as in preceding experiments, with this one exception that use was made of Anhydrous Eucerin (the Unguentum Alcoholicum Lanæ of the B.P.) instead of aquaphor or falba as the lanoline base.

The survivor guinea-pigs from the "KP" and "MP" series—7 in each—had received the first injections of their respective original courses of treatment forty-two weeks previously and their last injections thirty weeks before. During these thirty weeks they had put on weight and were in excellent condition. Both new series of guinea-pigs were from the same stocks as the previous series and at the commencement of the present experiment were almost full-grown. Standard conditions of housing and feeding, etc., apply to all three groups.

Results.—In the survivor group (*b*), of previously treated animals, the first 3 died of acute anaphylaxis (2 from "KP" and 1 from "MP"), within a few minutes of the first injection (1 ml.) of the new course. All the others survived this initial injection, though two exhibited sudden prostration, dyspnœa, and "shock" (body chilled, eyegrounds visibly blanched, etc.)—interpreted as anaphylactic. These recovered. The injections were repeated weekly for seven weeks in all, without any repetition of these acute anaphylactic features.

In this series, however, another interesting phenomenon was observed: at the time of the first injection of the present course of new emulsion, the original injection sites—even in the "KP" and "MP" animals—could be felt, readily enough, as flat button-like areas of induration in the abdominal wall. But five or six days later, these had all become greatly swollen, protuberant, soft and fluctuant. On sample needling of two of these from different animals, thin yellowish purulent fluid was obtained which proved sterile on aerobic culture. Despite this, the injection course was continued and most of these sterile abscesses subsided in the next five or six days. In three instances, however, there was sloughing of one or more of these lesions. This reaction—the Arthus phenomenon—was marked in both "KP" and "MP" series but was doubtful in the "B" and "N" series and would certainly

have been unsuspected had not its dramatic character and severity in the "KP" and "MP" groups led to closer scrutiny of this reaction.

None of the previously treated group (*b*) developed either clinical or (when eventually sacrificed) histological evidence of encephalomyelitis or other visceral disease. Nor, indeed, did they manifest the anorexia, loss of weight and general listlessness that usually occur in animals treated for the first time with brain emulsions.

That the new brain emulsion used was a potent one was, however, shown by the occurrence of 18 cases of gross paralysis with widespread histological features of acute disseminated encephalomyelitis out of 25 animals injected—i.e. 18 "positive" reactors in the "AO" group. In addition, there were 2 cases of mild transient paresis but these were not sacrificed and have been ignored in the final count.

That the "old" emulsion was still potent was conclusively shown by 10 cases of gross paralysis (associated, in all cases, with histological features of perivenular encephalomyelitis) exactly as in other "positive" series in the preceding two experiments.

TABLE IV.—OCCURRENCE OF LESIONS IN GUINEA-PIGS INJECTED WITH HOMOLOGOUS BRAIN TISSUE ("OLD" AND "NEW") IN EXPERIMENT III

Animal Number	*Day of onset of paralysis*	*Day of death*	*Presence of gross paralysis*	*Histological ECM lesions*
(*Old emulsion*) :				
W 1	12	12	+	+
W 2	none	14 (trauma)	none	none
W 3	21	30	+	+
W 4	31	34	+	+
W 5	31	34	+	+
W 6	31	34	+	+
W 7	35	37	+	+
W 8	35	37	+	+
W 9	35	44	+	+
W 10	43	48	+	+
W 11	57	58	+	+
(*New emulsion*) :				
AO 1	27	28	+	+
AO 2	30	32	+	+
AO 3	30	32	+	+
AO 4	30	32	+	+
AO 5	31	32	+	+
AO 6	31	32	+	+
AO 7	32	32	+	+
AO 8	34	41	+	+
AO 9	35	41	+	+
AO 10	37	41	+	+
AO 11	39	41	+	+
AO 12	39	44	+	+
AO 13	39	48	+	+
AO 14	39	50	+	+
AO 15	42	50	+	+
AO 16	43	50	+	+
AO 17	46	51	+	+
AO 18	47	51	+	+

In the present experiment, since the previous two experiments had provided a good stock of histological material for the study of the lesion, paralysed animals were allowed to live much longer than it had seemed prudent to risk in Experiments I and II. This led to some new experience being gained as to the range of survival time in this disease. Most of the "positives," then, in groups "W" and "AO" were killed usually when they were so completely paralysed as to be unable to move at all and when decubitus ulceration and rectal and bladder incontinence were, as a rule, present. Even at this stage, however, the animals were remarkably well in general health, had lost weight only moderately and were eating well. The development of general symptoms of illness—"broody" head, raised fur, fast breathing, fever, etc.—usually betokened pyelonephritis.

Consequently, in Table IV, which summarizes the results of this experiment, a double column has been used indicating, separately, the day of onset of paralysis and the day when killed.

Transmissibility tests from selected animals (*see* Section E) were negative.

EXPERIMENT IV.—*To test the effects in rats and in rabbits of repeated subcutaneous injections of sterile guinea-pig brain emulsion* (*in "adjuvants"*) *of known potency in guinea-pigs.*

It was seen, in Experiment I, that homologous brain emulsion in "adjuvants" failed to produce encephalomyelitis or other lesions in *rats*. But, likewise, this *rat* brain emulsion failed to produce encephalomyelitis in guinea-pigs. It seemed desirable, therefore, to ascertain whether the rat is truly insusceptible to "allergic" encephalomyelitis or whether the failure to produce lesions in the rat might be due simply to the absence of the encephalitogenic factor from rat brain.

In the present experiment, a guinea-pig-brain emulsion known to be encephalitogenic for guinea-pigs was used, not only against rats but also against rabbits. The test on rabbits was carried out simultaneously with Experiment II, the brain emulsion being the same as that used for the "B" group of guinea-pigs; the 12 rabbits used received 2 ml. weekly for ten weeks. The test on rats was carried out simultaneously with Experiment III, the emulsion used being the same as for the "AO" group of guinea-pigs; the 50 rats used received 1 ml. subcutaneously each week for six weeks.

Results.—(*a*) *Rats:* Not one single animal out of the 50 so treated has shown any neurological or other disorder during the whole course (150 days) of this experiment.

(*b*) *Rabbits:* Here, the results were remarkably reminiscent of those obtained by Weston Hurst using emulsions of sheep, human and monkey—but not guinea-pig—brain, and *without* "adjuvants"; similar, likewise, to those of Rivers, Sprunt and Berry and of Rivers and Schwentker. The histological changes which Morrison obtained in the rabbit using homologous brain tissue with "adjuvants" were not obtained here with guinea-pig brain and "adjuvants."

Briefly, instead of the fairly uniform onset, evolution, and clinical characteristics of the lesion in the guinea-pig, in the rabbit the reaction is capricious—sometimes wasting alone, sometimes an abrupt onset of a neurological disorder usually with epileptiform convulsions but unaccompanied by histological changes, and sometimes sudden death after a variable interval with no apparent cause at autopsy.

Five of the 12 rabbits showed no signs of illness at any time during the 240 days under observation. When finally sacrificed, autopsy revealed nothing abnormal and histological examination of the CNS, liver, spleen, adrenals and kidneys in all, was likewise negative. The injection sites in the abdominal wall were still seen as disc-like mounds with thick fibrous wall and inspissated, putty-like, content.

The other 7 died at widely scattered intervals :—

Rabbit 7 : Went off its food about 33rd day. Increasing wasting over next ten days but no neurological signs. On the 47th day, developed sudden severe generalized convulsions and died. There had been no paralysis or blindness.

Rabbit 5 : Went off its food about 40th day. Progressive wasting for ten days, then gradual improvement despite continuation of injections. Killed on 230th day. No pathological changes found at autopsy and histological examination of CNS showed no vestige of any lesion.

Rabbit 4: Did not show wasting. Suddenly, on the 57th day, it developed a well-marked encephalitic picture. It was found in the morning with its hind-legs splayed out and stiff, while voluntary movements of these limbs were slow, clumsy and spastic. The forelegs were weak and crumpled up beneath the weight of the body so that the animal fell forward on its nose. In the evening, it developed a continuous series of clonic convulsions which were violently exaggerated on the least stimulation of touch or noise. It was apparently blind. Autopsy showed no visible pathological changes in the viscera. The state of nutrition was good and the stomach even contained recently ingested food.

Rabbit 9 : Went off its food about the 140th day and became listless. On the 144th day it was sitting with head drooping on one side and nose almost touching the ground. The eyes showed no blink reflex. When taken from cage, it rolled over on its side, unable to stand up. Marked loss of weight.

Rabbit 6 : Not eating on 160th day. The 167th day it showed spastic paralysis of all limbs. Head drooping. No blink reflex in one eye and, in other, a purulent conjunctivitis. Autopsy showed marked wasting but no other visible pathological changes.

Rabbit 11 : Off its food on 170th day. Died suddenly on 173rd day in violent convulsions. Autopsy showed wasting but nil else.

The 7th animal remained until about the 200th day when it went down with bronchopneumonia and was killed without autopsy.

Careful histological search throughout the CNS of rabbits 7, 5, 4, 9, 6, and 11 failed to reveal any pathological features. Other viscera—liver, spleen, kidneys and adrenals, in all cases—proved likewise negative.

EXPERIMENT V.—*To determine whether, with guinea-pigs from stocks of known susceptibility, and with an antigenic emulsion of proved potency, it is possible to prevent and/or cure "allergic" encephalomyelitis by the regular administration of antihistaminic substances in maximal dosage.*

It will be seen in the discussion that the thesis has been advanced that the injection of brain tissue with "adjuvants" leads to several different and distinct reactions—including neurotoxic, allergic and general toxic ones not specifically active against the nervous system. And while it has been shown here that in rabbits, for instance, a guinea-pig-brain emulsion which is definitely encephalitogenic to guinea-pigs is only neurotoxic to rabbits, yet it seems from the work of Morrison that a homologous brain emulsion with "adjuvants" is not only neurotoxic but also encephalitogenic (i.e. in respect of the full-blown histological picture). Therefore, it seemed possible that in the production of "allergic" encephalomyelitis two factors might be responsible for the structural changes—(1) a possible cellular sensitization of the brain tissue (Kabat, for instance, suspects a derivative of myelin), and (2) the production of a factor responsible for the extreme venular dilatation, and exudation from these, which is the histological peculiarity of this lesion. It was thought that this second, or contributory, factor might be a histamine-like substance.

The consistently high incidence of "positives" in guinea-pigs in this type of work made it seem that a *prophylactic* experiment, using antihistaminics, could afford significant results. At the same time, antihistaminic *therapy* was tried in the established disease.

Fifty guinea-pigs received, regularly, six-hourly injections of Anthisan for the first 32 days—i.e. up to the day of the peak-incidence of lesions in this work—of the course of treatment with brain emulsions. Maximal dosage was aimed at

(determined on M.L.D. tests in normal guinea-pigs), and maintained to the limit of tolerance of the test animals. Histamine wheal tests were applied each week to 4 animals prepared with intraperitoneal trypan blue to confirm in these the presence of antihistaminic substance immediately preceding the Anthisan injection. There were a number of casualties from overdosage, and from traumatization to upper abdominal viscera (due to the fact that the brain emulsion had to be given into the thoracic and *upper* abdominal wall while the *lower* abdominal wall was reserved for the injection of the Anthisan four times daily). Toxicity was manifested by the frequent occurrence of convulsions after Anthisan injections and by the occurrence, in all, of marked apathy, anorexia and emaciation. And, finally, 11 in one pen of 25 succumbed to an intercurrent disease resembling pseudo-tuberculosis though no Pasteurella or other bacteria were isolated.

Of the 50 controls not treated with prophylactic antihistaminics, 8 developed typical disseminated encephalomyelitis by the 32nd day, but of the 50 Anthisan-treated animals only a small number of positives occurred onwards from the 32nd day—day on which the Anthisan had been stopped.

The results of this abortive experiment in prophylaxis are set out in Table V, but these are regarded as suggestive only—certainly not conclusive.

Therapeutic Experiment.—From the control series, after the onset of paralysis, numbers 9, 10, 15, 16, 17, 18, 19, and 20 were treated therapeutically with Anthisan injections six-hourly for five days (except No. 15—two days only); numbers 1, 2, 3, and 4 with Benadryl also six-hourly for two to three days; and numbers 12, 13 and 14 with Phenergan (N-betadimethylamino-n-propyl phenothiazine hydrochloride) once daily for five days.

The paralysis was not ameliorated in any one of these 15 animals by the antihistaminic therapy.

Section C

Transmissibility Tests—(Consolidated Results)

These were applied, in all, to 15 of the positive cases—5 from "B," 1 from "N," 6 from "AO" and 3 from "W." When paralysis was fully established and it was decided to sacrifice the animal, the brain and cord were removed with aseptic precautions as for the preparation of brain emulsions. A small piece of the spinal cord was cut off the specimen (the rest of which was fixed for histology) and mashed up in saline. The turbid saline supernatant was injected into healthy guinea-pigs, 3 being used for each test, 1 subcutaneously and 2 intraperitoneally. On three occasions intracerebral inoculations were also given, and twice intratesticularly. None developed any lesions, the animals in all instances being allowed to live for six to seven weeks before being finally sacrificed.

Section D

Clinical Aspects of Experimental "Allergic" Encephalomyelitis in Guinea-pigs—(Consolidated Data)

This description is based on over 75 animals with this lesion, in 18 of which a cinematograph record has also been made. In all the "positive" cases in Experiments I, II, III and V, the clinical manifestations have been remarkably constant. These may be grouped as follows :

(1) *Neurological manifestations.*—These are almost invariably the presenting, and often the only, signs of the disease. During the first few weeks of the course the animals remain active, then the first signs of motor weakness develop—invariably first in the hindquarters, and shown by a wobbly gait which progresses to gross paralysis which may take less than twenty-four hours or even up to ten days but commonly three or four days. Spasticity is manifest in most, the legs being held scissors-wise and taut, slightly to one side or the other. If the animal is frightened by a move to catch it, it pulls itself out of the way by using the

TABLE V.—RESULTS OF EXPERIMENT V.—ANTIHISTAMINIC PROPHYLAXIS

Control Series (50 guinea-pigs) Emulsion only WITHOUT Anthisan					Test Series (50 guinea-pigs) Emulsion, WITH Anthisan				
No.	*Day of onset of paralysis*	*Day of death*	*Histol. ECM lesion*	*Cause of death*	*No.*	*Day of onset of paralysis*	*Day of death*	*Histol. ECM lesion*	*Cause of death*
					1	—	4	0	Toxicity
					2	—	9	0	Peritonitis
1	24	26	+	Killed	3	—	13	0	Toxicity
2	27	28	+	do.	4	—	16	0	do.
3	30	32	+	do.	5	—	18	0	Empyema
4	30	32	+	do.	6	—	26	0	Toxicity
5	30	32	+	do.	7	—	29	0	Pyelonephritis
6	31	32	+	do.	8	—	30	0	Peritonitis
7	31	32	+	do.	9	—	31	0	Liver infarct
8	32	32	+	do.	10	—	32	0	Toxicity
					Six-hourly Anthisan stopped.				
9	34	40	+	do.	11	32	34	+	Killed
10	35	41	+	do.	12	34	38	+	do
11	35	Remission	?	—	13	—	36	0	Toxicity
12	36	42	+	do.	14	—	39	0	do.
13	36	42	+	do.	15	—	40	0	"Pseudo-tuberculosis"
14	37	41	+	do.	16	—	41	0	do.
15	39	41	+	do.	17	—	42	0	do.
16	39	44	+	do.	18	—	43	0	do.
17	39	48	+	do.	19	—	43	0	do.
18	39	50	+	do.	20	—	43	0	do.
19	42	52	+	do.	21	—	43	0	Perinephric abscess
20	42	52	+	do.	22	—	45	0	"Pseudo-tb."
21	43	50	+	do.	23	42	45	+	Killed
22	46	51	+	do.	24	—	45	0	"Pseudo-tb."
23	47	51	+	do.	25	—	46	0	do.
					26	47	50	+	Killed
					27	48	50	+	do.
					28	—	49	0	"Pseudo-tb."
					29	—	49	0	do.
					30	—	50	0	do.

52nd day : All survivors in both series sacrificed and experiment terminated.

forelegs only, the hindquarters being dragged along. When spasticity is complete, sustained clonus can often be readily elicited. Then in the next two or three days bladder and rectal incontinence appear, the former shown by the wet and soiled perineum, the latter obvious in the greatly distended anal canal with its presenting mass of unevacuated fæcal matter. When sacrificed (as usually the case) at this stage, the bladder is found greatly distended with urine which, not infrequently in those left to survive longer, is purulent.

A less common variant of the initial gait is that in which the weakness predominantly affects the adductor muscles of the hind limbs so that the animal

walks stiffly and clumsily with legs wide apart, occasionally subsiding between its splayed-out legs.

Though, as shown, the evolution of the paralysis may be prolonged up to ten days, it is the usual experience that once definite paralysis is established it always progresses till complete, with rectal and bladder incontinence necessitating sacrifice of the animal. Complete remissions, and remissions with relapses, do occur in a minority but only in animals which show milder initial signs—such as a slight paresis, or a slight unsteadiness in the gait. Because of the inconclusive character of borderline cases it was decided to exclude all cases of remission from the "positive" series. The incidence of complete remission is estimated to have been about 10 per cent. Remissions with relapses occurred only three times in the whole 75 positive cases.

Only rarely was a little weakness detected in the forelimbs of "positive" cases but never paralysis. Neck weakness, oculomotor paralysis, nystagmus or blindness have never been noted.

(2) *General features.*—Though the animals continue to eat well (even when completely paralysed) there is a tendency for all animals to lose weight during the 2nd and 3rd, and sometimes 4th, weeks, and thereafter they pick up weight even though the injections of emulsions are continued up to ten weeks. The loss of weight seems to be independent of neurological changes—for all animals, whether or not they ultimately develop encephalomyelitis, show this drop in weight. The paralysis, when it occurs, is not especially prone to occur in those which have lost weight. In fact, the paralysed animals have often been the most robust-looking animals in the various groups.

Neither the paralysed nor the unaffected animals show any fever or diarrhoea, and their coats remain thick and glossy.

That there develop immunity, anaphylactic, and local allergic (Arthus) reactions in all animals following injections of these brain emulsions has been shown in Experiment III.

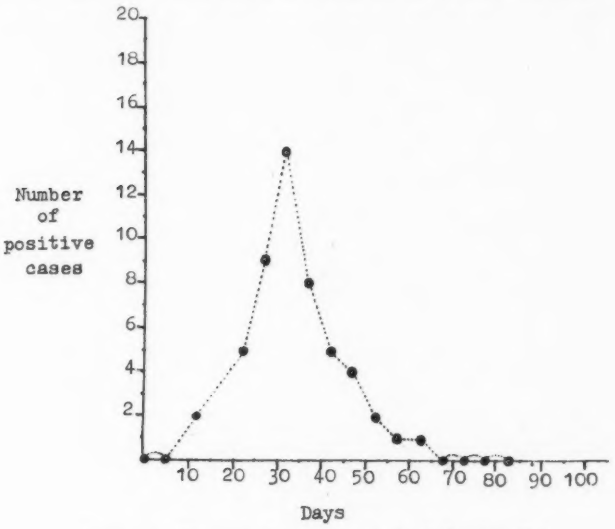
(3) *Local features.*—The injection masses in the abdominal wall rarely cause any evident discomfort to the animals. The mass, immediately after injection, may take the form of a smooth rounded mound, or a more diffuse swelling where the injection is deeper. As has been seen, these have been found *in situ* in guinea-pigs five months later, and would probably remain much longer if experience with the rabbits in Experiment IV is any guide (nine months). Occasionally, if the injection is too superficial, some of the material may run back through the track of the needle (of necessity a wide one). These injection masses remain sterile but when about four weeks old, necrosis of the overlying skin has sometimes occurred and the mass sloughed out. Thereafter, the tendency for this to occur diminishes. This tendency to local necrosis at the injection site seems to parallel closely the general toxic features already discussed.

Histologically (fig. 16), the local lesions are granulomata in relation to oil spaces, with foreign-body giant-cell reaction (non-follicular) and occasionally with a polymorphonuclear reaction even proceeding to suppuration.

The Time-Incidence of Lesions

The accompanying graph shows the consolidated data in 51 positives out of 91 animals injected in Experiments I, II, and III. It will be seen that there is a sharp peak-incidence about the 32nd day. Thereafter, the incidence falls off rapidly and the tail is not a long one. No positive has occurred after the 64th day despite continuation of the injection for a further three weeks and despite observation of the animals up to seven or eight months.

"ALLERGIC" ENCEPHALOMYELITIS
Time-Incidence of 51 *Positive Cases in* 91 *Guinea-pigs*
injected with Brain Tissue with "Adjuvants."
(No other treatment given in any of the series included here)



(Graph to illustrate final paragraph of Section D.)

SECTION E

THE HISTOLOGICAL FEATURES OF "EXPERIMENTAL 'ALLERGIC' ENCEPHALOMYELITIS" IN THE GUINEA-PIG

Methods:—Routine, for all material: Paraffin embedding. Staining with hæmatoxylin and eosin, and by Loyez' method; occasionally by Masson's trichrome stain and by Pappenheim's method for plasma cells.

Special, for positive cases under study: Frozen sections. Hæmatoxylin and Sudan III: Bielschowsky's technique for nerve fibres: Penfield's modification of Hortega's combined method for microglia and oligodendroglia.

Reticulum staining.

Findings.—In all positive cases the lesions are, without exception, readily seen and are remarkably constant. They consist of multiple foci of perivascular cellular proliferation disseminated throughout the whole of the brain and spinal cord. They occur with remarkable predominance in the white matter, though the grey matter is not entirely spared.

They are most abundant in the cerebrum where they occur always in the white matter and usually in the periventricular regions. They are particularly prone to be extensive at the lateral angles of the lateral ventricles, under the ependyma throughout the whole ventricular system, and in the tela chorioidea. The lower parts of the corona radiata, the internal capsules and the commissures are common sites for marked lesions. In these regions there is a tendency for the foci of cellular proliferation to spill over into the grey matter of the adjacent thalamus and basal ganglia but in no single instance in all of these 75 cases have any of these foci been seen in the cerebral cortex. Around the 3rd ventricle, and in the mid-brain, lesions are not uncommon and here discrimination between white and

grey matter is not evident, but in the cerebellum, again, the limitation of lesions to the white matter has been strict. In the case of the spinal cord, lesions are distinctly pre-eminent peripherally in the white matter, but occasionally a perivascular infiltrate round a vessel coursing through the white matter encroaches upon the adjoining horn of grey substance.

No lesions have been encountered in the peripheral nerves despite routine search for them in all animals from the series used in Experiments I, II and III. Not even in those animals which developed cerebral lesions following injections of peripheral nerve substance were any lesions detected in the peripheral nerves.

The cellular proliferations which constitute the "lesions" histologically are invariably perivascular though here and there a local series of sections may be necessary in a given instance to confirm this relationship. The cellular infiltration (*see below*) may sometimes be traced out of the white matter into the deep sulci at the base of the brain or to the periphery of the spinal cord, and there the infiltrate seems to "spill over" into the subarachnoid—so that the lesion is not entirely a leuco-encephalitis but also, to this extent, a meningo-encephalitis. But this meningeal infiltrate is always, by contrast, scanty and, as will be seen presently, tends to show a greater proportion of lymphocytic and other free mononuclear cells than is seen in the parenchyma.

Scrutiny of the vessels within the parenchyma shows that the cellular proliferations are invariably related to the veins and venules. Where a little cellular infiltrate is seen within the Virchow-Robin space of a small artery or of an arteriole (usually in the leptomeninges) this is of banal lymphocytic character unlike the perivenular "lesion."

These cellular proliferations in relation to venular walls are not simple infiltrations of small round (lymphocytic) cells within the Virchow-Robin spaces. For this perivenular infiltrate, which is the predominant feature of the histology, involves two distinct elements:—

First, there is a proliferation of cells on, or of, the thin walls of these vessels, resulting in a concentric (but *expanding*) thickening of the wall which may become 6 or 8 cell-layers thick instead of the normal thickness of a single layer of endothelial cells apposed to a fine adventitial supporting membrane containing a few adventitial-cell nuclei. This proliferation of cells does not involve the actual endothelium and there is never any narrowing of the lumen—indeed, the engorgement and dilatation of the veins and venules, often extreme, is one of the most characteristic features of this lesion. There is no sign of thrombosis. The cells undergoing proliferation are of apparently *mesenchymal*, or adventitial, character—cells with large spherical or ovoid nucleus with well-dispersed chromatin, unlike the nucleus of the lymphocyte. The cytoplasm is fairly abundant and these cells form a *continuum* which obliterates the pre-existing structure of the wall and fills the Virchow-Robin space, though the cells do not appear to lie free within this space (figs. 8, 9, and 10). In reticulum preparations (fig. 11) these cells can be seen to lie between delicate strands of reticulum but this latter element shows no appreciable increase and it seems as if the reticulum strands had simply been teased apart by the proliferating (or emigrating) cells. A certain proportion of small round (lymphocytic) cells does, however, occur here and there round some of the vessels, within the Virchow-Robin space, and is more marked in those cases which have survived longer. But the adventitial cell proliferation is always the predominant element, and often the only one present.

In lesions which present a more acute character, a small number of neutrophil polymorphs has occasionally been found outside the vein wall—even mingling with the proliferating microglia within the territory of the perivenular parenchyma (fig. 10), but in this guinea-pig material these cells are not commonly encountered and I have the impression they are distinctly more scanty than in the corresponding lesion in the monkey as judged from a comparative study of sections from monkey

[*Continued on page* 220.

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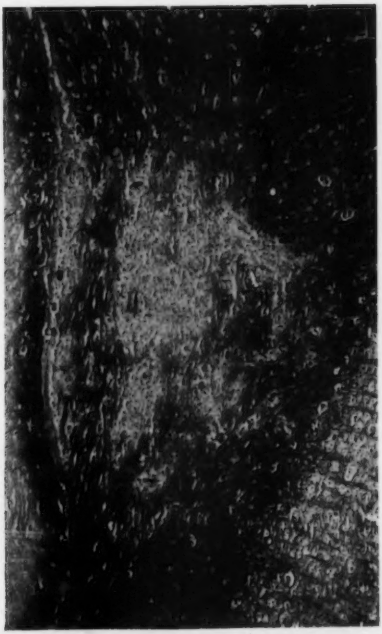

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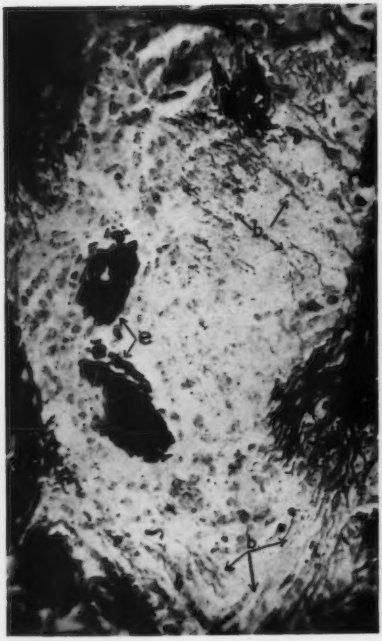

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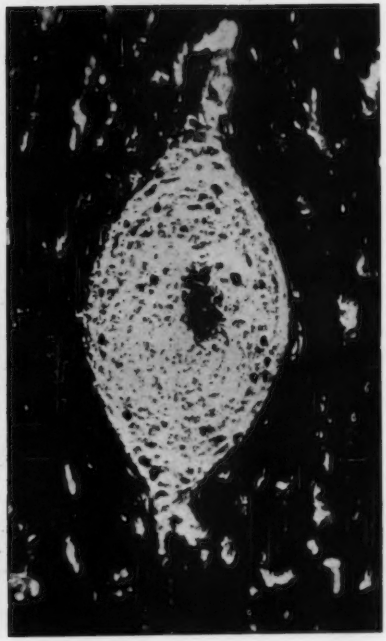

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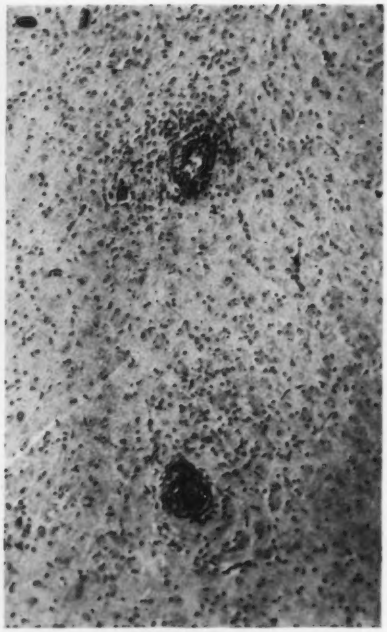

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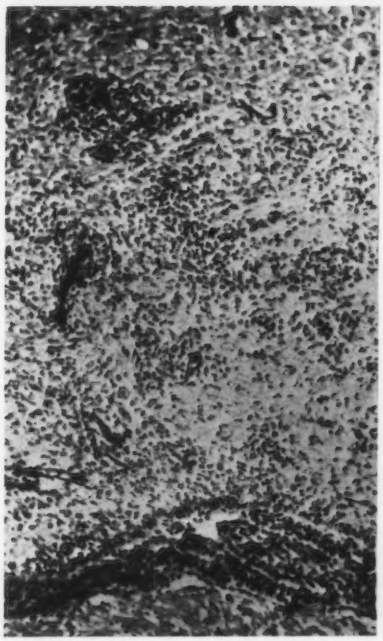

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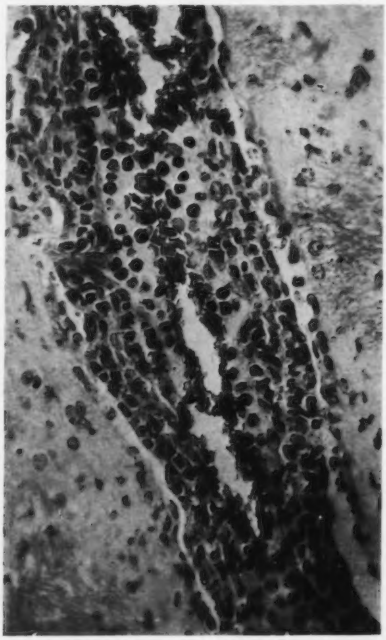

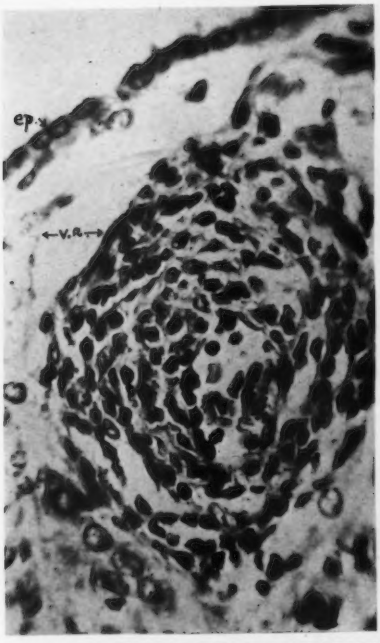

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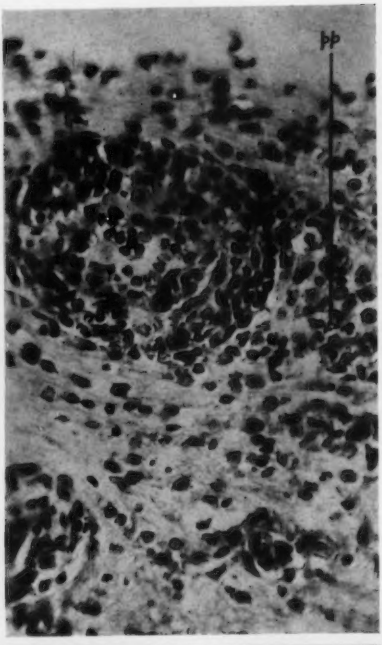

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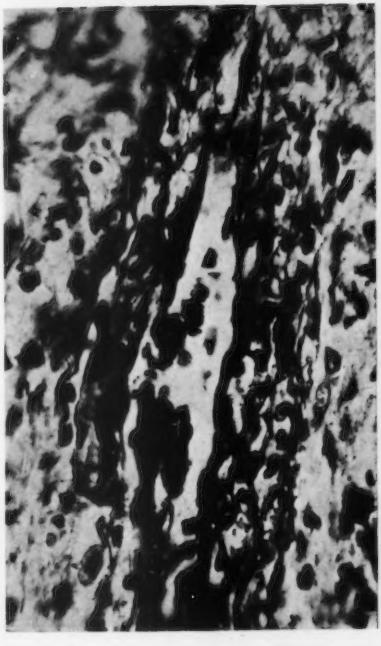

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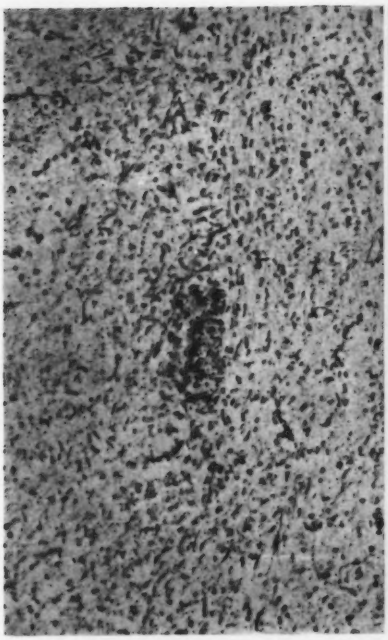

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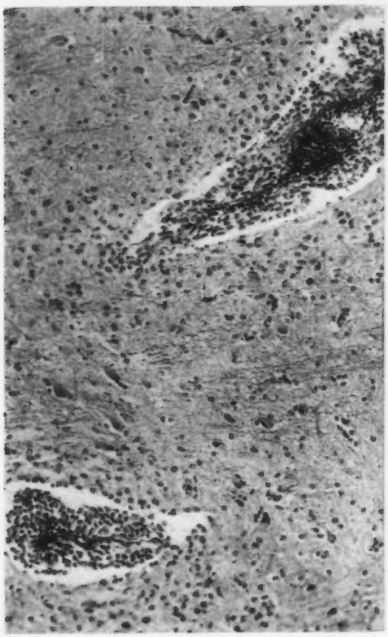

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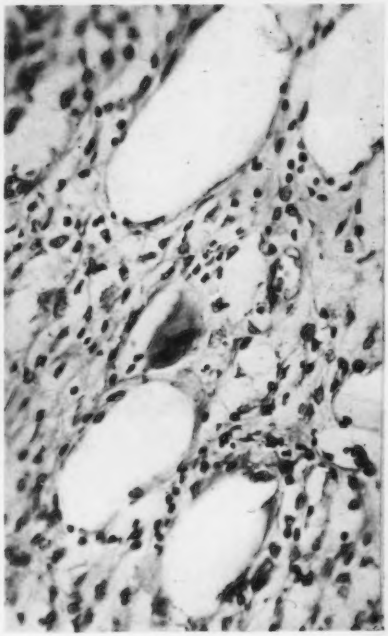

LEGENDS TO ILLUSTRATIONS

FIG. 1.—Guinea-pig brain KP5. Coronal section. Loyez' stain. ×6 diameters. Showing, within the ringed areas A and B, typical patches of demyelination in central white matter of cerebral hemispheres.

FIG. 2.—Field in ring "A" of fig. 1. ×60. Showing detail of demyelinated lesion within the white matter. Loyez' stain.

FIG. 3.—Brain of guinea-pig KP2. Right internal capsule. Loyez' stain. ×400. Perivascular demyelination. The masses of fixed R.B.C. within the lumina of the two venules at "e" stain intensely black. The large perivenular halo is not due entirely to the myelinated fibres being pushed aside by the proliferating adventitial cells but there is actual disintegration of myelin sheaths in the direction of the arrows at "b."

FIG. 4.—Guinea-pig brain KP1. Mid-commissure. Loyez' stain. ×260. A perivenular halo caused by pushing aside of the myelinated fibre bundles by the adventitial-cell proliferation. No true demyelination. The black mass in the centre is a cast of fixed R.B.C. in the lumen of the venule.

FIG. 5.—Guinea-pig brain KP2. Left internal capsule. Same magnification as fig. 4, for comparison, to show the "fuzzy" outline when there is actual myelin destruction.

FIG. 6.—Guinea-pig KP1. Thalamus. General topography of the perivenular lesions of which two are seen. Note the increased cellularity of the venule walls and the microglial increase in the surrounding parenchyma. H. & E. ×90.

FIG. 7.—Guinea-pig brain AO/12. H. & E. ×90. Centrum ovale. For comparison with fig. 6, to show the more confluent type of lesion with its merging fields of microglial proliferation. At the foot of the picture is seen the ependymal wall of the lateral ventricle and the chorioid plexus.

FIG. 8.—Guinea-pig B/10. H. & E. ×260. Internal capsule and caudate nucleus. View of a venule in longitudinal section showing *continuum* of proliferated adventitial cells.

FIG. 9.—Guinea-pig W/4. H. & E. ×460. Thalamus. Note ependyma at "ep." To show detail of "adventitial cell" proliferation. Note rouleaux of erythrocytes in lumen, the apparently intact and non-proliferated endothelium. Outside this are the proliferated "adventitial cells," 8 to 10 layers deep, "teasing apart the reticulum of the venule wall." The Virchow-Robin space, opened up by tissue shrinkage at "V.R.," is seen to be free of cells. No microglial proliferation in this instance.

FIG. 10.—Guinea-pig brain AO/16. H. & E. ×460. Similar features to fig. 9, but here there is also cellular increase within the perivenular parenchyma, including a rare example of two polymorphonuclear leucocytes (indicated by arrows).

FIG. 11.—Guinea-pig brain AO/9. Reticulum stain. ×460. Showing the proliferated "adventitial" cells lying enmeshed in strands of reticulum. The rouleaux of erythrocytes indicate the venule lumen.

FIG. 12.—Guinea-pig brain AO/9. Bielschowsky. ×920. At "V.R." is seen the Virchow-Robin space. The dark mass of cells, to the left of this, is the edge of the "*continuum*" of adventitial cells. The tissue to the right is the immediate perivenular parenchyma. This shows the persistent axons. Amongst these are scattered a few microglial nuclei.

FIG. 13.—Guinea-pig brain AO/11. Penfield's method. ×100. Showing the great perivenular increase of red cells and amœboid forms of microglia.

FIG. 14.—Post-vaccinial encephalomyelitis in man. Loyez' stain. ×90. For comparison with figs. 3, 4, and 5.

FIG. 15.—Post-vaccinial encephalitis in man. H. & E. ×90. Brain, showing two venules. Note the proliferating cells of the venule walls, and the microglial increase in the immediately surrounding parenchyma (cf. figs. 6 and 8).

FIG. 16.—Injection site in abdominal wall. Guinea-pig AO/9. H. & E. ×260. Showing the reaction caused by the injected emulsion. The spaces seen here contained paraffin and lanoline globules. The reacting cells are mainly histiocytes with occasional foreign-body giant cells, an example of which is seen in the centre of the field.

brains which both Dr. Kabat and Dr. Isabel Morgan have so kindly sent me. Plasma cells have not, however, been encountered at any time even in specially stained (Pappenheim) preparations.

The other element of the "lesion" is the microglial proliferation in the surrounding parenchyma, forming a halo two or three times the width of the vessel, and fading off insensibly into the normal parenchyma. This almost invariably accompanies the adventitial cell proliferation (fig. 6), scarcely ever being seen without it. When it is present, there is usually obliteration of the Virchow-Robin space.

In myelin preparations, this zone of microglial proliferation shows myelin disintegration which is usually complete in the vicinity of the vessel, but is incomplete and fragmentary at the periphery where it fades off into the surrounding white matter (figs. 1, 2, 3 and 5). The contours of the demyelinated zone are fuzzy and indistinct compared with a plaque of disseminated sclerosis. The myelin sheaths appear distinctly more vulnerable than the axis cylinders so that even in brains showing lesions with a tendency to rather wide haloes of myelin clearing (fig. 12), axis cylinders are generally preserved right up to the immediate proximity of the vessel. For all that, the impression has remained that this perivenular zone of myelin disintegration is *not* selective demyelination for Bielschowsky preparations do frequently show perivenular haloes of pallor corresponding in extent to the haloes in the myelin preparations. The technical problem is more difficult in the guinea-pig brain than in the human brain in which the axis cylinders are less slender.

Where the zone of microglial proliferation is absent—i.e. in those lesions where the changes are limited to the "adventitial cell" proliferation—there is no demyelination and the strands are merely pushed aside, as is well seen in fig. 4, by the swollen vessel wall.

The microglial proliferation in the perivenular parenchyma, when present, involves young amœboid forms and rod cells (the latter often in large numbers—*see* fig. 13), and full-blown "gitter" cells are conspicuously scanty. Even in cases in which paralysis has been present for a period of seven to ten days before sacrifice of the animal, compound granular corpuscles have been seen only scantily in Sudan and hæmatoxylin preparations. But the microglial nature of these rod cells and young amœboid forms is unquestionable in silver impregnations—showing, as they do, the characteristic narrow, elongated, often somewhat contorted, nuclei with condensed chromatin, and the branched cytoplasmic processes in successfully impregnated preparations: mitotic figures are sometimes seen.

Where the veins and venules are numerous and close together—as, for instance, in the subependymal regions between the caudate and thalamus, and below the basal ganglia—the zones of perivenular microglial massing frequently coalesce into more diffuse lesions (figs. 7, 1 and 2)—recalling the claim of Rivers and his colleagues (1935) to have produced a lesion simulating Schilder's disease. But even where this more extensive lesion forms in the guinea-pig brain, it is never malacic and in none of these 75 positive animals has there ever resulted any infarction, hæmorrhage, or cyst formation.

Recapitulation

The present experiments have shown that:—

(1) An encephalomyelitic lesion similar to that obtained by Kabat and his colleagues, and by Morgan, in monkeys, can be produced regularly in over 50 per cent of guinea-pigs, using sterile *homologous brain tissue* with "adjuvants."

(2) This lesion can be produced in these animals likewise by sterile *peripheral nerve tissue*, provided care is taken to ensure that the preparation be of strength comparable to that of the brain tissue preparations; this is contrary to the findings, in monkeys, of Morgan (1947) and of Kabat *et al.* (1948).

(3) The lesion in guinea-pigs has a definite period of incidence with a constant peak at the 32nd day.

(4) It is produced *only by nervous tissue*, and not at all by "adjuvants" alone, nor by "adjuvants" in conjunction with kidney, liver and muscle of comparable concentration.

(5) The disease produced is non-transmissible to other guinea-pigs.

(6) It does not respond to therapy with antihistaminic substances.

(7) An emulsion of sterile brain in "adjuvants" retains its encephalitogenic activity for a prolonged period.

(8) Guinea-pigs which survive an original course of injections with sterile homologous brain tissue in "adjuvants" have, or have acquired, an immunity to further treatment with fresh emulsions of brain tissue in "adjuvants" though they manifest general and local tissue sensitization.

(9) Rat brain with "adjuvants" *does not* produce lesions in guinea-pigs; nor will guinea-pig brain in "adjuvants" produce lesions in the rat; but guinea-pig brain in "adjuvants" may produce neurological manifestations in the *rabbit*.

(10) The central nervous lesions produced in guinea-pigs by this technique bear the following features:—

(A) They are *disseminated*, are *perivenular* in location, and *occur predominantly in the white matter*.

(B) They are characterized, *not* by any "encephalitic" reaction of leucocytes or lymphocytes (though these may participate in some measure), but by:

(*a*) a curious and profuse proliferation of the adventitial cells;

(*b*) partial softening of the immediately perivenular parenchyma, expressing itself in myelin preparations as a zone of demyelination;

(*c*) frequently—usually when "(*b*)" obtains—by a zone of microglial proliferation in the immediately perivenular parenchyma.

Discussion

The term "encephalomyelitis" is with justification applicable to this experimental lesion in so far as it fulfils both of Cohnheim's criteria of "exudatio" and "proliferatio." Despite this, it seems impossible that it is caused by any living agent, bacterial or virus, for these reasons: (1) the phenolized emulsions have been made and maintained bacterially sterile throughout, (2) direct transmissibility tests have been consistently negative, and, finally, (3) the incidence of the lesion throughout a series of experiments extending over eighteen months has been too constant for any cause so fortuitous as a spontaneous virus infection, even if this were the reactivation of a latent infection: and, further, the incidence of the lesion in the hands of other workers, as we saw in the introduction, is remarkably similar in guinea-pigs to that obtained here.

Further, though an "encephalomyelitis," this experimenal lesion lacks the histological features of an infective encephalomyelitis—for polymorphonuclear leucocytes and lymphocytes participate only rarely in the infiltrate, appearing only in older lesions and possibly (as probably also, for instance, in disseminated sclerosis) in response simply to the parenchymatous degeneration. But, in any case, this hæmatogenous element of the infiltrate is invariably subsidiary to the adventitial cell and microglial proliferation and never dominates the histological picture as it does in all the acute encephalitides of known virus or bacterial origin.

It is precisely in this latter characteristic that this experimental lesion resembles the post-exanthem encephalomyelitis of man (*see* footnote). For in this latter group of diseases (so singularly uniform amongst themselves in clinical and histological characteristics whether initiated by vaccinia, variola, varicella, morbilli, rubella, or scarlatina), it is not alone the demyelination and perivenular microglial massing (fig. 14) which are so characteristic but also those peculiar changes in the venular walls illustrated in fig. 15—a crowding and teasing apart of the adventitia by mesenchymal cells with only a minor accompaniment of hæmatogenous lymphocytes and monocytes. Between the experimental lesion and the human post-exanthem lesion there is, if anything, a *quantitative* difference only —viz. that in the human lesion, at least of the post-vaccinal and post-measles forms which have been my main source of comparative study, the adventitial cell proliferation does not attain to the broad *"continuum"* which I have described in the guinea-pig. In this regard, however, it may be pertinent to recall Babes and Mironesco's description of a "wide

Note.—A careful distinction must be drawn between true post-exanthem encephalomyelitis and disseminated phlebothrombosis occurring in the brain (as sometimes in other organs) in the course of whooping cough, pneumonia, sometimes in measles, etc.

embryonic zone of small elongated cells," occurring perivascularly, in the lesion of the post-paralytic accident of antirabic treatment.

But the zone of "demyelination," or "myelinoclasis," in the guinea-pig is somewhat less marked than it is in the human post-exanthem lesion, though it is still present (figs. 3 and 5). In the monkey, it would appear from the descriptions of Morgan, Kabat, Ferraro and others, that this zone is more intense than it is in the guinea-pig—more strictly comparable, then, in this animal to that of the human lesion.

It has been insisted, in Section E, that in the guinea-pig lesion the perivascular halo in myelin preparations is not, however, truly *selective* demyelination. Axis cylinders are damaged too—a point with which Jervis and Koprowsky concur. The change in the perivenular parenchyma is indeed one of "softening"—which indeed was the description, it may be recalled, that Turnbull himself used in his classical paper on the post-vaccinal lesion in man—with the more vulnerable sheaths being somewhat more extensively damaged than the axons. In fact, even in the human post-exanthem encephalomyelitis the terms "demyelination" and "myelinoclasis," which it has been customary—following Perdrau—to attribute to it, are misleading. The axis cylinders, too, are damaged. Spielmeyer himself insisted: "Die ganze Nervenfaser, Markscheide und Achsenzylinder, zugrunde geht."

In conclusion, the analogy between the experimental lesion and human encephalomyelitis, even having regard to possible fallacies in arguing from the experimental animal to man, *is far too close* to be insignificant. No other natural process in the brain, either in the animal or in man, possesses these histological peculiarities. And having regard to the fact that the experiment in man provided by post-Pasteur-treatment paralysis forms a bridge between the animal experiment and the post-exanthem human lesion, it may reasonably be claimed that the lesion of "post-exanthem encephalomyelitis"—whatever its underlying mechanism—has been experimentally reproduced.

Whether the experimentalist has succeeded in reproducing disseminated sclerosis is a totally different question and one which will be discussed in a later paper devoted to a study of that disease. Meanwhile, it is my personal impression that we have not yet reproduced disseminated sclerosis. For in the experimental lesion, as in the post-exanthem lesion in man, the contours of the perivenular "myelinoclastic" zone, albeit fairly clear, are fuzzy in comparison with the abrupt contours, "découpés comme à l'emporte-pièce," of a plaque of disseminated sclerosis. It is possible (though the evidence is that it must happen extremely rarely) that the post-exanthem lesion might initiate the process of disseminated

sclerosis but before it does so a new pathological phenomenon must develop.

The immediate problem is concerned with the ætiology of the experimental encephalomyelitis. What is this chemical agent in brain tissue which alone, or when suitably activated, is capable of initiating disintegration of the parenchyma (preferably of the white matter) around the small veins and venules? Surely, for one thing, we cannot hypothecate a spasmodic mechanism in those very veins and venules which of all such vessels in the body are characterized by their absence of any muscular coat. Nor, for another thing, have we been accustomed to regard the walls of veins and venules, even the peculiar cerebral veins and venules, as membranes of respiratory and metabolic exchange. Yet it seems to me that the whole histological picture in the spontaneous human lesion, as in the experimental lesion, points to the direct passage, through the venular wall, of some irritant agent.

Do the experiments so far conducted give any clue to the chemical nature of this irritant? Little so far; but implicit in most of the published work on this experimental lesion has been the assumption that the reaction is an "allergic" phenomenon—a hypothesis which has indeed been advocated now for many years in the spontaneous human post-exanthem lesions and in disseminated sclerosis notably by Pette in Germany and by Ferraro in America.

However, this assumption, as it affects the experimental lesion at the moment, is possibly not valid.

First, it has been shown here in this work on the guinea-pig, that four types of reaction do undoubtedly occur in these animals following repeated subcutaneous injections of sterile homologous brain emulsion in "adjuvants": (*a*) a general toxic reaction, (*b*) sensitization (anaphylaxis and the Arthus phenomenon), (*c*) an immunity reaction, and (*d*) the encephalitogenic effect. These four reactions are not obviously associated. In fact, they appear to be *dissociated;* for the general toxic and the encephalitogenic reactions occur at different times and not necessarily in the same animals; and sensitization may be manifested without the encephalomyelitic effect—indeed, even in animals which are or have become immune to this effect.

Secondly, by the same token, the *in vitro* demonstration of antibodies and allergens in such animals with lesions must be interpreted with caution. Undoubtedly, they can (as serological evidence would seem to show) develop "antibodies to brain" but it does not follow that brain lesions when they occur in these animals are caused by circulating "antibodies to brain." *Animals without brain lesions also develop the circulating antibodies to brain.*

Thirdly, if we are dealing with a lesion secondary to a cellular sensitization, this sensitization is one which is remarkably non-specific: it may appear with homologous brain tissue (even after a single injection) and, heterologously, with a very wide range of species as has already been pointed out. On the other hand, the reaction does not appear to be part of any general isoallergic phenomenon, for it does not occur in other organs following injections of tissue from these organs administered in the same way.

And, finally, if the lesion be a manifestation of "allergy," the sensitizing antigen in the brain tissue must be one which is chemically remarkably stable—withstanding, as Kabat has shown, treatment by physical agents like boiling and ultrasound, and by chemical agents like formalin—so that, if a protein, it can act in denaturated state.

Clearly we must seek in the immediate future to fractionate the emulsion and to trace the active agent, while at the same time trying to ascertain whether fractionation and extraction will abolish the side-effects like the general toxicity, the sensitization and the antibody formation. Likewise, too, the enhancing or catalytic effect of dead acid-fast bacilli demands early elucidation.

Furthermore, since there is such a close parallelism between this experimental lesion and human post-exanthem encephalomyelitis, it is an attractive hypothesis that this latter lesion is due not to the virus of the original disease but to some *chemical* derivative of the skin rash (whether or not sensitization is involved), a chemical substance closely allied to, if not identical with, the chemical derivative of brain and nerve tissue which is responsible for the experimental lesion. Though, as we have seen, emulsions of liver, kidney and muscle with "adjuvants" do not produce any lesion comparable to those caused by nervous tissue, it may well be that the *skin* contains the encephalitogenic factor. Unfortunately, it has not yet been found possible to prepare an adequately homogenized emulsion of skin comparable to the other organ emulsions used; but if it can be shown, for instance, that desiccation of tissue does not damage the encephalitogenic factor, or if experiments at present being conducted should show that the factor can be extracted by a suitable solvent, it may prove possible to extract from the skin the same, or a similar, encephalitogenic factor as is present in the brain and in the peripheral nerves.

I have pleasure in acknowledging my gratitude to Dr. Elvin A. Kabat, New York, and to Dr. Isabel M. Morgan, Baltimore, for kindly sending me sections of their experimental monkey material for comparative study, and for providing me with samples of aquaphor and falba.

I am greatly indebted to Burroughs Wellcome Biological Laboratories for providing me with heat-killed *M. tuberculosis* which have been prepared from the same strain throughout all this experiment; also to Messrs. May & Baker for supplies of Anthisan and Phenergan, and to Messrs. Parke, Davis & Co. for supplies of Benadryl.

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THE ORBITAL GYRI[1]

BY

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I.—Introduction

The purpose of the present investigation was to study the functions and connexions of the orbital gyri which have long remained obscure (fig. 1). Ruch and Shenkin [16] found that ablation of the orbital surface (area 13) in monkeys is followed by pronounced hypermotility—spontaneous movements sometimes increasing five to ten times after bilateral lesions. Since the anatomical connexions of these gyri are unknown, we have undertaken in the present study to trace functional connexions by the method of physiological neuronography [13]. We have also studied the responses of this area to electrical stimulation in cats, dogs, and monkeys. In 1894 Spencer, an associate of Sir Victor Horsley, observed in cats, dogs, rabbits, and monkeys that faradic stimulation of the orbital gyri caused arrest of respiratory movements as well as marked fluctuations in the blood pressure. Spencer's paper, however, was largely forgotten until Bailey and Sweet in 1940 [3] confirmed and extended his observations. More recently they have also been confirmed by Delgado and Livingston [6].

Methods

Our data are derived from experiments on nine cats, three dogs, and twenty monkeys (nineteen *Macaca mulatta* and one *Cercocebus fulginosus*). The experimental methods may be divided into: (i) those experiments in which the orbital gyrus was stimulated electrically, (ii) those using strychnine neuronography, and (iii) those which were designed to study afferent pathways to the orbital gyrus.

(i) *Electrical stimulation.*—The animals used in this group consisted of four cats, three dogs, and thirteen monkeys. The following anæsthetics were used:

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[2]National Research Council Fellow, 1947–1948.

[3]Honorary Fellow in Physiology, Yale University School of Medicine, 1947–1948.

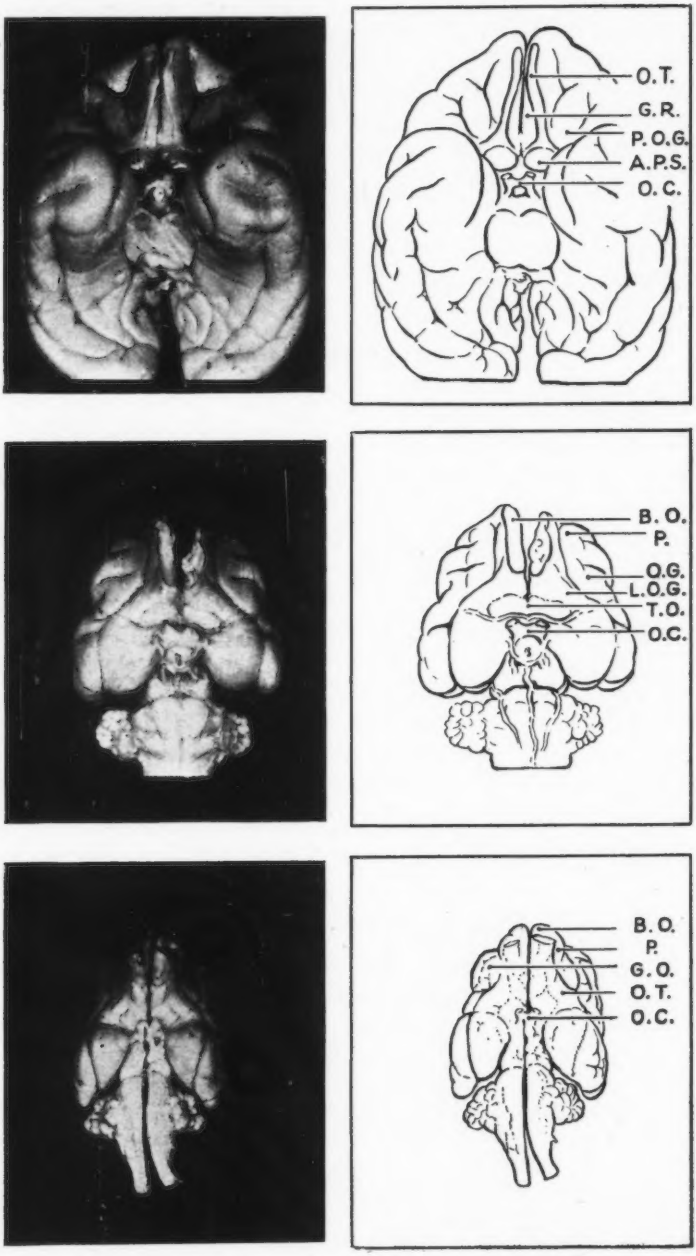

FIG. 1.—Top, monkey brain; middle, cat brain; bottom, dog brain. A.P.S., Anterior perforated space. B.O., Olfactory bulb. G.R., Gyrus rectus. L.O.G, Lateral olfactory gyrus. O.C., Optic chiasm. O.G and G.O., Orbital gyrus. O.T., Olfactory tract. P., Prorea. P.O.G., Posterior orbital gyrus. T.O., Olfactory trigone.

Dial (15 animals), nembutal (1 animal), sodium pentothal with curare (4 animals). The posterior orbital cortex was exposed by two different approaches: either by enucleation of one eye, exenteration of the orbit, and exposure of the brain through an orbital roof craniotomy, or by a wide frontal craniotomy, ligation of the sagittal sinus, division of the falx at the cribriform plate, and placing the animal on its back so that the frontal lobes fell away from the orbital plate. In some cases the orbital surface was not exposed, but was stimulated transcortically by bipolar electrodes, separately insulated and bared only at the tips (which were one millimetre apart); these were directed by the Horsley-Clarke stereotaxic instrument. Stimulation was performed either with the Goodwin thyratron or a square-wave, uni-vibrator stimulator built by Mr. Alexander Mauro,[1] with which the frequency, pulse duration, and intensity could be varied independently. Frequency of stimulating current as well as intensity was determined by means of a cathode-ray oscillograph. Blood pressure was recorded by a cannula in the femoral artery connected through a fluid-filled tube to a tambour or a mercury manometer. Respiration was recorded by a pneumatic cuff about the chest, an air amplifier, or a tube connected directly to the tracheal cannula with a constant source of oxygen in a closed system. The animals were heparinized, or given "Fastusol pink," to prevent coagulation in the arterial cannula. Mineral oil was kept on the cortex to reduce evaporation during prolonged experiments (24-60 hours).

(ii) *Strychnine neuronography.*—Four monkeys were used in this part of the study. Small squares of filter paper saturated in 3 per cent strychnine sulphate were applied to the posterior orbital cortex through the orbital roof. The animal was held in the Horsley-Clarke stereotaxic instrument, and two bipolar electrodes, each with the tips one millimetre apart, were placed at various points in order to explore the deeper structures extending from the medulla to the frontal lobes. Simultaneous, push-pull, differential amplification and recording was used, leading off from the bared tips of bipolar electrodes, as well as from one pole of each of two bipolar electrodes which were four millimetres apart. Cortico-cortical connexions were not studied except between the two orbital gyri of opposite hemispheres. Nembutal anæsthesia was used because it gave a smoother base line of electrical activity. In all cases recording was done simultaneously from the site of strychninization as well as from the exploring electrodes. Positive firing was not considered unless the spikes were 100 per cent synchronous with the reference electrode at the strychninized site, and unless there were approximately the same number of spikes in the exploring electrode as in the reference electrode. Electrolytic lesions were made at each point of firing before moving the electrodes from a given needle tract. The animals' heads were perfused immediately after death with saline and formaldehyde, and the brain fixed in formalin. Serial sections were made 10 micra thick, and every twentieth section was stained by Nissl's technique. In some cases firing occurred between the two bipolar electrodes, but not at either one alone. In these instances lesions were made at both electrode sites, and the areas between the lesions were studied microscopically.

(iii) *Study of afferent pathways.*—In a series of five cats and one monkey, the experiment of Bailey and Bremer [2] was repeated, using the "isolated encephalon" preparation for the cats. Ether served for the exposure of the orbital cortex and the vagi and, following spinal section at C1, the animal was maintained on artificial respiration. The experiment on the monkey was carried out entirely under nembutal with the aid of Dr. H.-T. Chang. In every experiment exact conditions of Bailey and Bremer's observations were repeated. Keeping the cortex bathed in mineral oil proved to be an excellent expedient by which we could prevent drying of the cortex and also minimize spread of the stimulating current.

[1]To be described.

II.—Results

Electrical Stimulation

Blood pressure responses.—In the cat, dog, and monkey, stimulation of the posterior part of the orbital gyrus caused alterations in the blood pressure. Under Dial anæsthesia (0·6 c.c. per Kg. of body weight), stimulation in almost all cases caused a drop in the blood pressure coinciding with the application of the stimulus. Slower rises following a few seconds' delay were less frequently encountered even though using the same parametres of stimulation. We agree with Bailey and Sweet [3] that rises in blood pressure are more readily obtained in the monkey than in the cat.

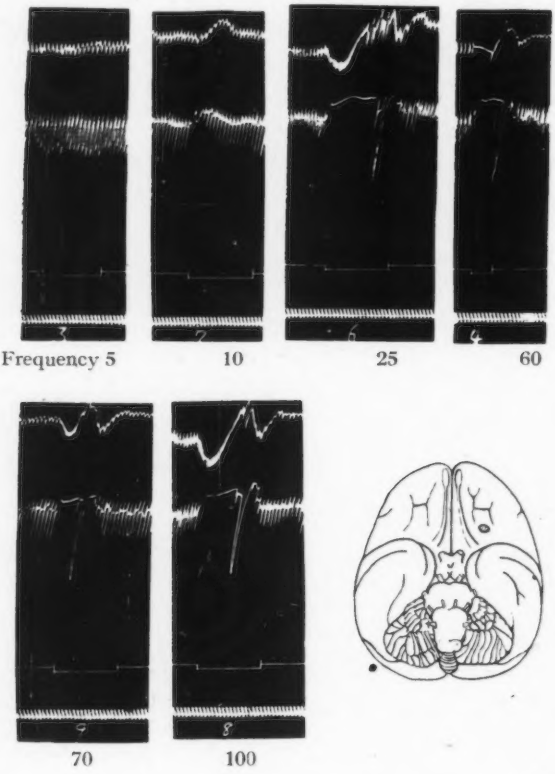

Fig. 2.—Electrical stimulation of the posterior orbital gyrus of the monkey using different frequencies. Upper line, blood pressure. Second line, respiration. Third line, duration of stimulus. Fourth line, time, in two-second intervals. The numbers below the time signal are those of successive stimuli, while beneath each kymograph strip are the frequencies used during each stimulus. In the respiratory tracings, the upstroke is expiration. Note that there is no effect at five per second, there is a rise in blood pressure at ten per second, while above these frequencies there is an initial fall and secondary rise of blood pressure.

Although the tendency of the blood pressure is to fall instantly when a threshold stimulus is applied under Dial anæsthesia, we noted that under curare, stimulation of the orbital surface almost invariably caused a rise in blood pressure.

Through variation of frequency of stimulating current, it was repeatedly possible in monkeys to raise or lower the blood pressure at will,

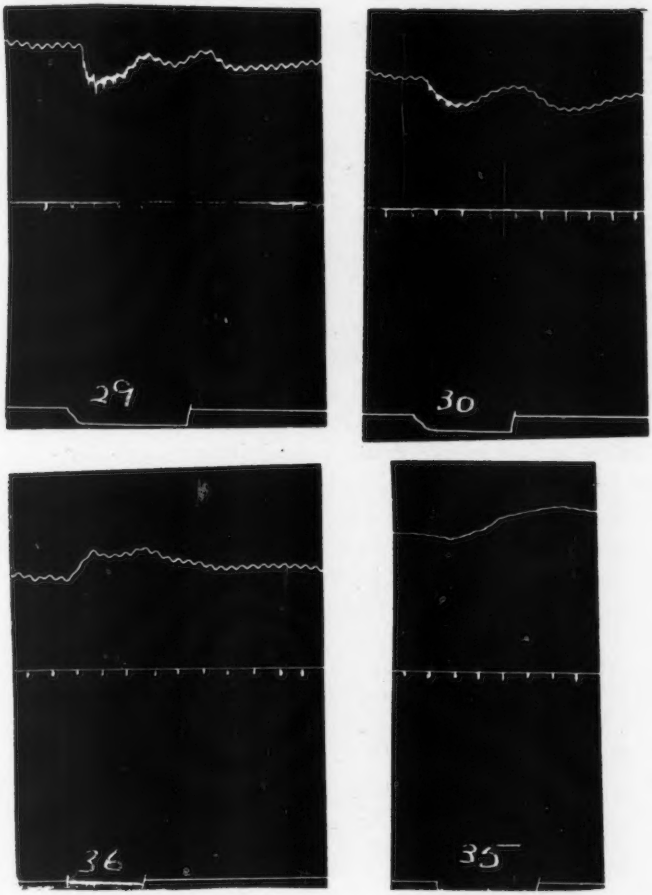

FIG. 3.—Electrical stimulation of the orbital gyrus of a monkey, varying only the wave form in two different loci. Nos. 29 and 30 show drops in blood pressure from two different points in the orbital surface when using square wave stimuli. Nos. 36 and 35 show rises in blood pressure from the same two loci as above when using "spikes" from the Goodwin thyratron. Stimuli Nos. 29 and 36 are at the same point in the orbital gyrus, while Nos. 30 and 35 are in a different spot, two millimetres anterior, in the orbital gyrus.

the electrode being kept at exactly the same focus (fig. 2). In one experiment on a curarized monkey, two different wave forms were used from two different stimulators, one of which produced square waves and the other waves of almost instantaneous rise with a logarithmic falling phase. In this animal, variation of the wave form only, while the frequency and intensity were held constant, caused a reversal of the blood pressure response: falls in blood pressure were associated with the square wave stimulus, while the "spikes" caused the reverse effect at the same intensity (fig. 3). The pulse duration of the individual wave was varied from 0·1 to 20 milliseconds. This variation caused no reversals in responses, and the optimal effects on blood pressure were obtained with from 5 to 10 millisecond pulses.

In a number of monkeys it was possible to localize the area from which blood pressure responses could be most readily obtained without other effects. In these experiments care was taken to use a threshold stimulus just sufficient to obtain a definite effect on the blood pressure. Careful mapping showed a most sensitive locus in the posterior part of the posterior orbital gyrus in the monkey corresponding to the posterior part of Walker's Area 13 [19]: area FF of von Bonin and Bailey [5]. If, when using minimal stimuli, one moved from this area as much as one millimetre, the blood pressure response failed to occur. In these instances the entire orbital surface was explored and with the exception of the small area noted, no blood pressure changes were produced.

The anterior perforated space was stimulated in five monkeys (fig. 1). The changes in the blood pressure obtained from this area were in many instances the reverse of those from the posterior orbital gyrus. Changing the frequency of the stimulus also reverses the response obtained from each area. When low frequencies (10 per sec.) caused a rise in blood pressure from the orbital gyrus, a drop was obtained from the anterior perforated space. Similarly, when high frequencies (60 per sec.) caused a drop in blood pressure in the orbital gyrus, rises were obtained from the anterior perforated space (fig. 4).

The finding that strychninization of the posterior orbital gyrus "fires" the caudate nucleus (*see* below) was evidence that the orbital gyrus might be a suppressor area. We therefore performed an experiment[1] in which cortically induced movements were subjected to the influence of a concurrent stimulus of the orbital gyrus. In no instance was inhibition of a somatic response observed. In a further search for possible suppression of cortical electrical activity, it was again stimulated electrically, but no

[1]We wish to thank Drs. Margaret Lennox and Rembrandt Dunsmore for their help in this experiment.

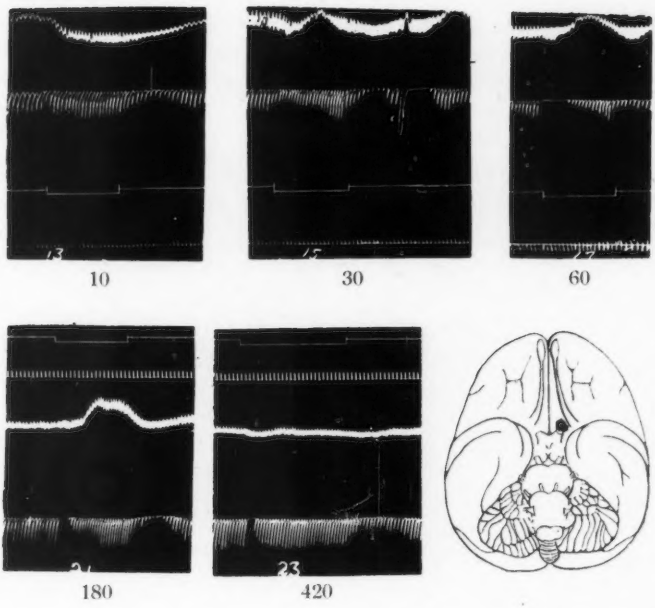

FIG. 4.—Electrical stimulation of the anterior perforated space at different frequencies. The large numbers below each kymographic strip represent the frequency of stimulus used. Upper line, blood pressure. Second line, respiration. Third line, stimulus marker. Fourth line, timer, in two-second intervals. Fifth line, stimulus numbers. Sixth line, frequencies used during each stimulus, in cycles per second. Note that there are slight drops in blood pressure at 10 and 30 per second, while at 60 and 180 there are rises. Compare with fig. 2 to see reversals in effect in these two areas. For frequencies 180 and 420 the stimulus marker and time signal are lines one and three, the blood pressure and respiration lines three and four.

reduction in the electrocorticogram was obtained, although distinct suppression could be effected from Area 24, a well-known suppressor area.

Respiratory responses.—Spencer [18], Smith [17], Bailey and Sweet [3], and Delgado and Livingston [6] have all demonstrated that respiratory arrest or inhibition could be obtained by stimulation of the orbital gyrus in cats, dogs, rabbits, and monkeys. In our experience also this was the almost invariable result of such stimulation. We have found that arrest of respiration could be obtained without alteration of the blood pressure, and blood pressure could be altered without affecting the respiration. Delgado and Livingston also mentioned that in one instance they had a rise in blood pressure without change in respiration on stimulation of the posterior part of the orbital gyrus, and they repeatedly produced respiratory arrest without alteration of the blood pressure. The separation of

these two phenomena is sometimes difficult to attain and is not always predictable. Usually we were able to excite the effects independently by moving the bipolar stimulating electrode as little as 1–2 millimetres from the most sensitive locus (fig. 5).

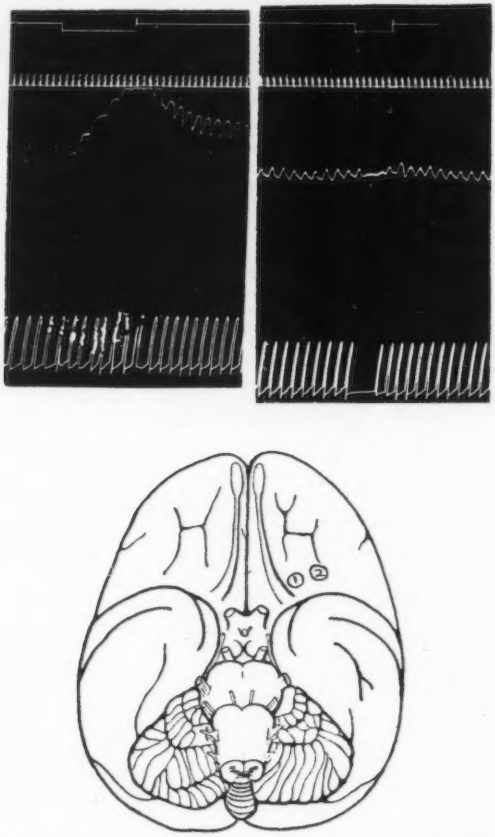

FIG. 5.—Electrical stimulation of two slightly different points in the posterior orbital gyrus, showing the independence of the blood pressure and respiratory effects. Upper line, stimulus marker. Second line, timer, in two-second intervals. Third line, blood pressure. Fourth line, respiration. The left-hand record is from point "1" on the diagram, while the right-hand record is from point "2."

Blood pressure changes and respiratory arrest were obtained after bilateral cervical vagotomy (two animals), after bilateral splanchnicectomy (two animals), after bilateral destruction of the paraventricular nuclei of the hypothalamus (one animal), and after bilateral adrenalectomy (two animals). In one monkey, diminished but definite blood pressure changes

were obtained following three paralysing doses of tetra-ethyl-ammonium chloride (Etamon).

Smith [17] raised the question of whether the rise in arterial pressure might not cause the simultaneous arrest of respiration which usually accompanies the stimulus. He therefore removed both carotid sinuses and both carotid bodies, but still obtained the respiratory arrest. He secured further evidence of the independence of the two phenomena by stimulating the anterior composite gyrus (orbital gyrus) of the cat when the respiratory activity was paralysed by curare, and still obtained the vascular response. We have confirmed the latter observation.

Respiratory arrest was invariably in the expiratory position, and the respiratory cycle could be inhibited in any phase of its development [6]. We have found that complete arrest of respiration could be obtained in the cat, dog, and monkey. The question arose whether the arrest of respiration might not have released enough adrenalin to cause the associated rise in blood pressure, but removal of both adrenal glands shows that this effect is independent of adrenal gland secretions.

Stimulation of the anterior perforated space resulted in the same type of respiratory response as that from the orbital gyrus (fig. 4) although in many instances there was a delayed inhibition as well as the immediate effect.

Pupillary responses.—Stimulation of the orbital gyrus was generally associated with dilatation of the pupils. Hodes and Magoun [9] have shown this to be due to inhibition of the oculomotor nucleus rather than to sympathetic stimulation. Pupillary dilatation was more readily obtained, however, from the anterior perforated space than from the orbital gyrus.

Eye movements.—In the majority of experiments, vague, wandering eye movements were observed concurrently with the stimulus. Usually these were deviations toward the side stimulated, but no relation to the frequency, intensity, or wave form of the stimulus was observed.

Somatic responses.—In many cases, when the anæsthesia was light, stimulation of either the orbital gyrus or the anterior perforated space was associated with vague, coarse motor movements of the extremities. For some time we were troubled by this and wondered whether spread to motor areas had occurred or whether the animal might be experiencing pain since deepening the anæsthesia eliminated the motor movements and allowed the autonomic responses to remain. These effects persisted, however, even with the use of mineral oil as an insulating liquid through which the electrodes were plunged to stimulate the cortex. The crucial experiment proved to be one in which we placed pledgets of cotton, soaked in 3 per cent procaine solution, on the cortex at the site of stimulation. This

completely abolished the autonomic responses as well as the motor movements, indicating that the effect originally obtained was not due to spread of current. When the procaine wore off, the responses returned, and reapplication again eliminated them. On plunging the electrodes through the anæsthetized cortex the responses reappeared unaltered. We believe therefore that these motor movements elicited from the orbital gyrus are truly neural in origin and cannot be attributed either to current spread or reaction to pain.

Other autonomic effects.—In some cases, when the condition of the animal was ideal and the anæsthetic level was suitable, distinct lacrimation and salivation were evoked during stimulation of the orbital gyrus. No quantitative or objective measurements of these responses were made. In several instances the gastro-intestinal tract was observed directly through a laparotomy incision during the course of stimulation of the orbital gyrus, but no movements or inhibition of movements were observed.

Physiological Neuronography

Four monkeys were used in this part of the study. In all cases strychnine was applied to the posterior part of the posterior orbital gyrus of a monkey held in the Horsley-Clark instrument. Two bipolar electrodes four millimetres apart, each with the tips one millimetre apart, were used to study the diencephalon starting posteriorly and moving anteriorly in vertical needle tracks two millimetres apart until the level of the strychninization was reached. In different animals various groups of co-ordinates were explored in order to cover as many structures as possible. In two animals the homolateral connexions were studied, and, in one of these two, both hemispheres were thoroughly explored for homolateral connexions from the orbital gyrus. In the other two monkeys only the contralateral connexions were investigated. A total of 2,351 points was studied in the four monkeys. In no instance have our findings been in disagreement with those of Mettler [15] or Ward and McCulloch [20]. These latter observers found projections from the posterior orbital gyrus of the macaque monkey to the paraventricular nucleus and the posterior hypothalamic area. Our electrodes did not enter these nuclei; hence we have no further evidence concerning these connexions. Our results can be summarized as follows (fig. 6):

Hypothalamus.—(i) Strychnine spikes were observed when recording between two electrodes which straddled the median forebrain bundle [1]: (ii) Firing also occurred when the two electrodes straddled the H Field of Forel; (iii) In the anterior hypothalamus, just posterior to the anterior commissure, connexions were demonstrated to the lateral preoptic area magnocellularis [1].

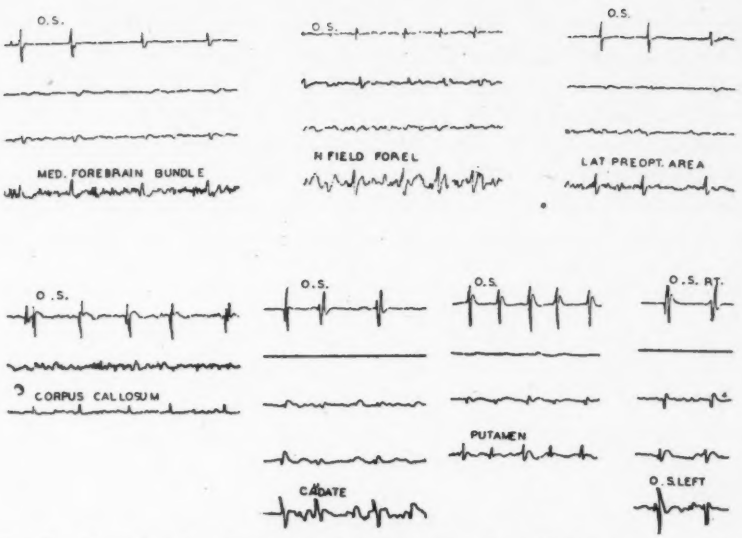

FIG. 6.—Records taken during strychninization of the orbital gyrus in monkey. The electrode in which strychnine activity is observed is labelled in each case. Top tracing (o.s.) is reference electrode at site of strychninization.

Putamen.—Strong firing was found throughout most of the homolateral putamen as far forward as the level of strychninization. Connexions were also found to the contralateral putamen, especially in its most ventral portion. Firing was also observed at the anterior ventral extremity of the internal capsule where it borders on the putamen. Whether this indicates there are fibres going into the internal capsule at this point is not yet clear, but this site of firing was consistently observed.

Corpus callosum.—Firing was found in the posterior part of the corpus callosum in one animal.

Caudate nucleus.—Firing was found in the contralateral caudate nucleus but, oddly enough, not in the homolateral.

Orbital gyrus.—Connexions were readily demonstrated from the strychninized orbital gyrus to its fellow on the opposite side.

Afferent Pathways

In 1938, Bailey and Bremer reported that "stimulation of the central end of the vagus nerve increases the electrical potentials of the orbital surface of the frontal lobe of the cerebral cortex." No other portion was affected. Their experiments were on cats prepared as we have described above. In a number of animals we have attempted to repeat this experiment. In five cats and one monkey, out of a larger series of animals used,

particularly significant negative results were obtained. Other animals of this series were discarded as "insignificant negatives" for one reason or another such as faulty anæsthesia, shock, etc. However, at no time did we observe any increases in the frequency or amplitude of the electrical potentials of the orbital surface of the frontal lobe, the gyrus proreus, or the ectosylvian gyrus. We are unable to offer an explanation of our inability to repeat the results of these experienced and distinguished observers and, in our view of this, it would seem desirable to investigate this question further.

III.—Discussion

The fact that with different anæsthetics different effects on the blood pressure follow from stimulation of the orbital gyrus is not surprising. Bailey and Sweet [3] obtained rises in blood pressure from this area when using Nembutal, whereas Delgado and Livingston [6] usually got falls in blood pressure when they used Dial anæsthesia. Spencer, using ether, with or without morphine, usually obtained rises in blood pressure. Lund [12] finds that Dial inhibited vasopressor reactions but not those of vasodilatation. Laidlaw and Kennard [10] showed that barbiturates caused a dilatation of the capillaries of the hypothalamus in the region of the paraventricular and supra-optic nuclei, while causing a relative constriction in the cortex. On the other hand, they found that ether caused a relative constriction of the blood supply to the hypothalamus, but a vasodilatation in the cortex. Since we find evidence of orbito-hypothalamic projections as have Ward and McCulloch it is not surprising that those drugs, e.g. the barbiturates, which act on the hypothalamus, should affect reactions from the orbital surface. Hodes and Magoun [8] found (cats) that under Nembutal they could not obtain dilatation of the parasympathectomized iris, or piloerection. The evidence suggests that the barbiturates selectively abolish the excitability of the hypothalamus. We may therefore deduce that the falls of blood pressure from stimulating the orbital gyrus under Dial are due to a selective block, but that the rises obtained with curarized animals are the more normal reactions of this area.

The experiment most difficult to explain is that one in which merely changing the wave form from square waves to rapidly rising ones with an exponential falling phase, resulted in reversals in blood pressure responses when the intensity and frequency were kept constant. Rather than offer an hypothesis to account for this, we shall merely state that these changes in the parametres of the stimulus may result in changes in responses, and that in the future the stimulus characteristics should be carefully controlled. These variations in current may well account for the inconstancy in the results obtained by different observers [11].

The mechanism and pathway of the impulses causing the blood pressure responses must be varied and complex. Since it is possible to obtain these effects after vagal and splanchnic section and after removal of the adrenals and carotid sinuses and carotid bodies [17] and also after destruction of the paraventricular nuclei of the hypothalamus, it can only be concluded that the impulses are not mediated solely by these mechanisms.

The somatic responses which we obtained by stimulation under light anæsthesia, but which were abolished by topical application of procaine, are of interest, particularly in view of the relationship of this area to hyperactivity [16]. The fact that we have shown connexions to the caudate and putamen further implicates these structures in the phenomenon of hyperactivity, the mechanism of which is still obscure.

Our strychnine studies have shown new connexions which add to the body of knowledge of the frontal efferent pathways. The functional significance of the projections to the caudate, putamen, the Field of Forel, and the median forebrain bundle remain to be elucidated.

Summary

(1) The functions and connexions of the orbital gyrus have been studied in a series of cats, dogs, and monkeys.

(2) Electrical stimulation of the orbital gyrus affected blood pressure and respiration, the effects varying with the anæsthesia, the frequency of the stimulus, and the wave form of individual current pulses.

(3) Blood pressure and respiratory effects were obtained independently.

(4) The excitable area for these various autonomic responses corresponds to Area 13 of Walker, or "FF" of von Bonin and Bailey, and within this area there are discrete foci of maximal sensitivity.

(5) Stimulation of the anterior perforated substance is usually followed by a rise in blood pressure and respiratory arrest, as well as pupillary dilatation.

(6) Varying the frequency or the stimulus in the orbital gyrus and in the anterior perforated space may reverse the blood pressure reaction.

(7) Dilatation of the pupil, eye movements, salivation, lacrimation, and coarse motor movements were obtained by stimulation of the orbital gyrus and the anterior perforated space.

(8) The blood pressure and respiratory responses could be obtained after section of both vagi, the splanchnic nerves, and after removal of the adrenals, and destruction of both paraventricular nuclei of the hypothalamus, and after paralysing doses of tetra-ethyl-ammonium chloride.

(9) No suppression of somatic movements or of ECG could be obtained.

(10) Strychnine neuronography demonstrated connexions to both homolateral and contralateral putamen, contralateral caudate nuclei, corpus callosum, H Field of Forel, median forebrain bundle, and lateral preoptic area, as well as the contralateral orbital gyrus.

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SOME OBSERVATIONS UPON THE OTOLOGICAL EFFECTS OF STREPTOMYCIN INTOXICATION

BY

M. R. DIX, C. S. HALLPIKE AND M. SPENCER HARRISON

INTRODUCTION

THE subject of vestibular nystagmus has long been of interest to otologists and neurologists, in particular the nervous mechanism of its characteristic slow and fast components. It has been established that when such nystagmus results from labyrinthine stimulation or imbalance, the slow phase is its primary component and is mediated by impulses passing to the eye-muscles from the vestibular nuclei. Considerable obscurity still surrounds the mechanism of the rapid component which was at one time considered to be of cerebral origin (Wright, 1947). This view has, however, been recognized as untenable as a result of the demonstration by Bauer and Leidler (1911) and De Kleyn (1939) that induced vestibular nystagmus with a normal fast component is obtainable in decerebrate preparations, both animal and human.

According to Bárány (1907) and Lorente de Nó (1933) the rapid component is mediated by a short reflex pathway associated with the vestibular nuclei and lying within the substantia reticularis. Dohlman (1938) too, favours a close anatomical association of the rapid component mechanism with the vestibular nuclei.

Our interest in the relationship between vestibular and optokinetic nystagmus owes a great deal to the extensive investigations of Ohm (1922) and Ter Braak (1936). Ohm stressed the fact that both forms of nystagmus exhibit an identical rhythmic alternation of slow and rapid components and considered this an indication that both must depend upon some common anatomical mechanism. This conception he was able to support experimentally by means of his demonstration that nystagmogenic stimuli sumultaneously applied to the retinæ and labyrinths cause a nystagmus which exhibits a smooth summation of the optokinetic and labyrinthine elements, and in later papers Ohm (1936) claims to have identified the common nervous mechanism of the two responses with the vestibular nuclei themselves.

It follows that if Ohm's view of such a common mechanism is correct, then both types of response would be abolished by the destruction of these

nuclei, and it is the purpose of this investigation to ascertain whether this event, which is now believed to result from streptomycin intoxication (Winston, J., *et al.*, 1948), does in fact cause a common abolition of these two types of nystagmus.

Material and Methods

The clinical material for the investigation has consisted of a number of patients, 12 in all, who had undergone systematic streptomycin therapy for tuberculosis. Clinical particulars of these patients, with details of their streptomycin dosage, are to be found summarized in Table III. All were submitted to a careful examination of the ears, nose and throat, and a pure tone audiometric test of cochlear function. The nystagmic responses to vestibular stimulation were investigated by means of the caloric test technique described in 1942 by Fitzgerald and Hallpike.

In addition, the optokinetic responses were investigated by means of a rotating drum of improved design.

We have also carried out a systematic investigation of the galvanic responses in these subjects.

The results of the galvanic tests have been of particular interest since this type of vestibular stimulation is now considered to depend upon the integrity of the vestibular nuclei and eighth nerve, and not upon the vestibular sense organs in the labyrinth (Huizinga, 1931).

In carrying out these tests bipolar stimulation was used, the current being passed between brine-soaked pads firmly located upon one or other of the mastoid processes and the manubrium sterni. The tests were carried out with the patient standing with eyes closed and the feet and heels close together. The reaction was described as positive when swaying, which normally occurs towards the ear carrying the positive electrode (anode), could be clearly and repeatedly observed. Corresponding observations were also carried out with the polarity reversed; in these circumstances, of course, the direction of the swaying was also reversed. This part of the investigation will be discussed first.

To begin with, a series of control observations was carried out upon twelve normal individuals with no history of ear disease or vertigo. In all of these it was found possible to observe positive responses with values of current lying between the range of 0·3 to 1·9 ma., with an average value of 0·8 ma. Full details of these findings are given in Table I, while corresponding results of our observations in the series of patients subjected to streptomycin therapy are given in Table II. In both tables the figures given are for milliampères of current at threshold. The maximum currents given in Table II were determined by the onset of the usual painful sensations from the skin areas underlying the electrodes.

TABLE I.—12 NORMAL SUBJECTS
Ear stimulated

Case No.	*Right Polarity*		*Left Polarity*	
	−ve	*+ve*	*−ve*	*+ve*
1	0·6	0·3	0·6	0·6
2	0·5	0·45	0·5	0·45
3	0·5	0·5	0·4	0·6
4	0·5	0·7	0·5	0·7
5	1·0	1·0	0·5	1·2
6	0·45	0·4	0·45	0·4
7	1·4	1·5	1·4	1·5
8	1·0	1·3	1·0	1·4
9	0·5	0·7	0·5	0·7
10	0·45	0·4	0·45	0·4
11	0·6	0·6	0·55	0·55
12	1·8	1·9	1·7	1·8

TABLE II.—12 SUBJECTS FOLLOWING STREPTOMYCIN THERAPY
Ear stimulated

Case No.	*Right Polarity*		*Max. current used*	*Left Polarity*		*Max. current used*
	−ve	*+ve*		*−ve*	*+ve*	
1	0·5	0·5		0·5	0·5	
2	Absent	Absent	3·5	Absent	Absent	3·5
3	Absent	Absent	5·0	Absent	Absent	5·0
4	Absent	Absent	5·0	Absent	Absent	4·5
5	Doubtful	Doubtful	2·5	Doubtful	Doubtful	4·0
6	Absent	Absent	5·0	Absent	Absent	5·0
7	Absent	Absent	4·0	Absent	Absent	4·0
8	Absent	Absent	3·0	Absent	Absent	5·0
9	Absent	Absent	4·2	Absent	Absent	5·0
10	Absent	Absent	4·75	Absent	Absent	4·5
11	Absent	Doubtful	4·5	Absent	Absent	4·5
12	Absent	Absent	5·0	Absent	Absent	5·0

It will be seen that in all except one case a very severe reduction of the galvanic responses was found to have occurred in the streptomycin group of subjects, a finding which may be considered as strong evidence that in 11 of the 12 cases streptomycin had a toxic action upon the vestibular neurones, its point of action being either upon Scarpa's ganglion and the peripheral vestibular fibres, or upon the vestibular nuclei themselves. A later reference will be made to the preservation of the galvanic responses in this twelfth case.

The results of the investigation in the streptomycin group of the nystagmic responses to vestibular and optokinetic stimulation can be described very briefly.

(1) *Optokinetic nystagmus.*—This was present and normal in all directions in all 12 subjects.

(2) *Vestibular nystagmus.*—In 7 of the 12 subjects caloric nystagmus was absent. In 4 it was reduced. In 1 case only the responses approximated to normal. This, and the finding in this same subject of a normal galvanic response, may be taken to indicate that for some unexplained reason a relatively slight toxic action on the vestibular system had resulted from the streptomycin therapy.

The complete results of the investigation are tabulated below.

TABLE III

Case No.	*Disease*	*Daily dosage (grammes)*	*Duration of dosage (months)*	*Caloric responses*	*Opto-kinetic responses*	*Galvanic responses*
1	Pulm. T.B.	2	4	? Normal	Normal	Normal
2	Pulm. T.B.	2	5	Absent	Normal	Absent
3	Pulm. T.B.	1	6	Reduced	Normal	Absent
4	Pulm. T.B.	1	6	Reduced	Normal	Absent
5	Pulm. T.B.	2	4	Absent	Normal	Doubtful
6	Pulm. T.B.	1	6	Absent	Normal	Absent
7	Pulm. T.B.	2	4	Absent	Normal	Absent
8	Pulm. T.B.	2	4	Much reduced	Normal	Absent
9	Pulm. T.B.	2	4	Much reduced	Normal	Absent
10	Pulm. T.B.	2	5	Absent	Normal	Absent
11	Pulm. T.B.	2	4	Absent	Normal	Absent
12	T.B. meningitis	0·8–0·9	9	Absent	Normal	Absent

COMMENTS AND DISCUSSION

The results of our investigation show a marked dissociation of caloric and optokinetic nystagmus, the former being substantially abolished by streptomycin therapy and the latter wholly preserved. If, therefore, we accept the evidence of Winston and others that streptomycin destroys the vestibular nuclei, then it follows that the central pathways of optokinetic nystagmus, contrary to the view of Ohm and Ter Braak, are entirely independent of these nuclei.

A schematic representation of the functional anatomy of these pathways is given in the diagrams which follow (fig. 1).

It will be seen that, according to Ter Braak and Ohm, the common pathway of nystagmogenic impulses from the labyrinths and retinæ includes the vestibular nuclei (fig. 1A).

The correct arrangement, based upon our own findings, would appear to be as shown in fig. 1B. According to this, the common pathway is a shorter one, extending only from the gaze centres in the brain stem which control conjugate movements of the eyes to the eye muscles, and does *not* include the vestibular nuclei. Whether or not independent gaze centres

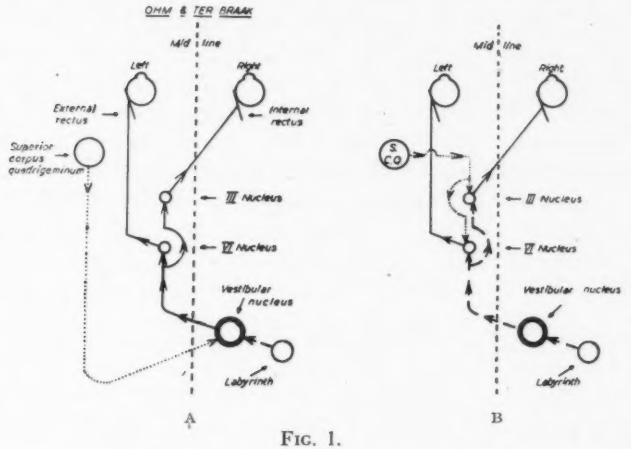

FIG. 1.

exist for the mediation of these retinal and labyrinthine impulses is not yet apparent.

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HEREDITARY STENOSIS OF THE AQUEDUCT OF SYLVIUS AS A CAUSE OF CONGENITAL HYDROCEPHALUS

BY

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CONGENITAL hydrocephalus occurs with sufficient frequency to be of lasting interest to clinicians and pathologists alike. According to Kovats [20] the incidence of this condition is about 1 in every 1,500 births. A large number of pathologically verified cases have been reported. Usually the mechanism of the hydrocephalus has been a demonstrable obstruction of the cerebrospinal fluid circulation. In some cases the obstruction was in the aqueduct of Sylvius, and in others at the foramens of Luschka and Magendie; in a third group an Arnold-Chiari malformation has resulted in displacement of the foramens of Luschka and Magendie into the cervical spinal canal and in a fourth group the subarachnoid spaces at the base of the brain was obliterated. The relative frequency of these different types of hydrocephalus is not known. Dandy [8] stated that about half of his congenital cases were due to stenosis of the aqueduct, but in our own material hydrocephalus with the Arnold-Chiari malformation is considerably more frequent than aqueductal stenosis.

The most commonly demonstrated ætiology of congenital hydrocephalus has been an inflammatory fibrosis of the meninges at the base of the brain and either an obliteration of the subarachnoid spaces around the brain-stem or occlusion of the foramens of Magendie and Luschka. Less often an associated ependymitis has caused a narrowing of the aqueduct. But aside from this group and those in which an Arnold-Chiari malformation resulted in a mechanical displacement of the 4th ventricle and basal foramens there are other cases in which the cause was not apparent. In some of the latter the aqueduct of Sylvius was narrowed or the foramens of Magendie and Luschka had not developed. Some writers have proposed that these represent developmental anomalies whereas others have argued for an intra-uterine meningitis or ependymitis.

The observation of the same abnormality in several members of one

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family has provided support for the idea that congenital hydrocephalus may be determined by an hereditary factor. The first reference to such familial incidence is in the textbook of Winckel [50] in 1893. This author cites, without giving the exact source of his information, the cases of Goehli where 6 congenital hydrocephalic infants were borne by the same mother; of Frank where one woman had had 7 congenital hydrocephalic infants; and of Castelli in which two hydrocephalic infants occurred in the same family. Other notable examples of multiple hydrocephalic births are the cases of Allingham [1] in which a woman had 3 spontaneous abortions, 1 full-term and 3 premature infants each with congenital hydrocephalus, and 5 normal infants; of Popham [34] who described a family in which a man had 2 children, one with spina bifida and the other with congenital hydrocephalus, by his first and an anencephalic monster with talipes by his second wife; of Wiener [49] where the first and third born infants had congenital hydrocephalus; of Straub [42] in which there were 2 normal infants, one with hair-lip and clubbed hands and feet and 2 with congenital hydrocephalus; of Iraeta and Harguindeguy [18] where 2 hydrocephalics were born to one mother; and of Kovats [20] in which 3 of 4 female infants had had hydrocephalus at birth.

Unfortunately post-mortem examinations were not performed on these cases. The only instance of familial congenital hydrocephalus with a report of the pathological findings is that of Ford [13]. This was a congenital hydrocephalic infant whose maternal aunt had had 2 children who died at an early age with enlarged heads. At autopsy no obstruction of the cerebrospinal fluid pathways could be demonstrated and the writer was inclined to attribute the ventricular enlargement to a hypersecretion of cerebrospinal fluid by the choroid plexuses.

In the past year we have received for examination[1] the brain of a hydrocephalic newborn male infant in which there was stenosis of the aqueduct of Sylvius. All of the male children of this family and 4 of 6 males in the preceding generation had been born with hydrocephalus. The cause of the ventricular enlargement was so well defined and the family history so remarkable that we are prompted to report it in some detail.

Report of a Case

Family history.—The patient, a full-term male infant, was the fifth of 5 children born to a white female of Swedish extraction. The first (born June 9, 1940) and third (born November 21, 1941) and fourth (born July 1, 1944) were normal females

[1]These clinical data were made available to us through the courtesy of Dr. Justin Anderson. For the general pathology findings and the neuropathological material we are indebted to Drs. D. A. Nickerson and Judd Sparling.

now living and well. The mother of the patient was one of 10 children, 6 males and 4 females. The first, third, seventh and ninth were congenital hydrocephalic full-term male infants who died at birth following ventriculostomy to permit delivery. The eighth was a normal full-term male infant, now living and well at 23. The fifth was a full-term, supposedly normal male infant who was stillborn "with the cord around his neck." The remaining four were normal full-term females. The second died of pneumonia at ten months. The fourth (mother of the patient), eighth and tenth children are living and well at the age of 30, 27, and 17 respectively. None of the mother's siblings have had children. There was no history of other congenital abnormalities in the maternal line within the memory of the patient's maternal grandparents, both of whom are living and well. In the paternal line there was no history of hydrocephalus, either congenital or acquired. However, the paternal grandmother had one brother born with a meningocele who died "with fever and convulsions" at the age of 7 months. The father of the patient was the first of 2 male children, both of whom are normal; their ages are 30 and 22 respectively. The latter has had no children. This pedigree is presented in fig. 1.

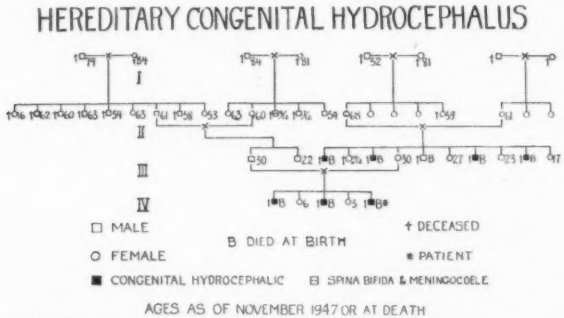

FIG. 1.—Pedigree chart of 7 male congenital hydrocephalics in two generations.

Maternal history.—The mother of the patient, a 30-year-old white female, was admitted to the hospital on May 17, 1947. The past history was negative except for rheumatic fever at 6 years with apparent complete recovery, and tonsillectomy. The four previous pregnancies (all full-term) were uneventful except for nausea and vomiting. The first and third infants, both hydrocephalic males, were stillborn following ventriculostomy for cephalopelvic disproportion. The mother recalled having craved cold water during both these pregnancies, but none during the second and fourth. There was nausea and vomiting throughout the present pregnancy and again an abnormal craving for cold water. Fœtal movements were perceived at four months and were very active throughout the remainder of the pregnancy.

Examination.—The patient appeared to be in good health. The pregnancy was calculated to be approximately at full term. The fœtal head was abnormally large with the left occiput anterior, and unengaged at pelvic inlet.

Laboratory data.—The blood and urine were normal. The blood Hinton was negative. The blood was type "A" and Rh positive. An anterior-posterior X-ray of abdomen and pelvis revealed a large fœtal head with widely separated suture lines and marked cephalo-pelvic disproportion.

Course.—The labour pains which were mild and irregular ceased on the second day and recurred on the third day. The cervix was fully dilated but the presenting head was still unengaged. On the third day a spinal needle was inserted through the anterior fontanelle into the lateral ventricle and 420 c.c. of cerebrospinal fluid

was removed under considerable pressure. The fluid was clear but became blood-tinged and finally grossly bloody as the flow ceased. A living male infant weighing 9 lb. 2 oz., was delivered by application of mid-forceps. The post-partum course of the mother was uneventful and she was discharged on May 28, 1947.

The infant did not cry until fifteen minutes after birth. He was not observed to be cyanotic at that time but respirations were irregular. Aside from the large collapsed head there were no other abnormalities. On the second day of life the left arm and leg were observed to be "spastic." The infant nursed poorly and regurgitated almost all of the milk formula. On the third day there were definite cyanosis and on the fourth day the abdomen became quite distended. The temperature rose to 102-103° F. at this time and continued to be elevated in the succeeding days. On the eighth day the jaws were rigid; the trunk and limbs were stiff. The infant was irritable, cried when disturbed, and moved very little. Rotary nystagmus and opisthotonus were present on the ninth day. The head remained collapsed. From the tenth to twelfth days the condition of the patient became worse. Death occurred on the thirteenth day (June 1, 1947).

Pathological Findings

Gross.—The body was that of an approximately full-term male infant. There were no abnormalities of the eyes, ears, nose or mouth. The skull was enlarged and the bones overlapped; in this partially collapsed state the circumference was 40 cm. There was a small needle puncture in the skin over the anterior fontanelle. No other external abnormalities were noted.

The peritoneal, pleural and pericardial surfaces were smooth and glistening. The ductus venosus and urachus were closed. The heart was normal. The lungs were heavy and their basal portions were purplish in colour and non-crepitant. The upper lobes were grey and subcrepitant. The cut surface dark, red, firm granular areas were found in both lower lobes. The bronchi were injected and contained mucoid material. In microscopic sections the bronchial lumens were filled with epithelial debris and small numbers of neutrophilic leucocytes. The alveoli near the bronchi contained large numbers of neutrophilic leucocytes. The alveolar walls were infiltrated with similar cells.

The spleen was normal in size and its capsule of purplish hue. On microscopic examination the architecture was well preserved. The pulp was congested and there were scattered macrophages containing hæmosiderin pigment. Occasional foci of erythropoiesis were found.

The liver was grossly normal and the only microscopic changes were vacuolization of the liver cells nearest the central vein, small amounts of hæmosiderin pigment in Kupffer cells and scattered nucleated red corpuscles in sinusoids. No foci of erythropoiesis were seen.

The gastro-internal tract, pancreas, adrenal glands, kidneys, urinary bladder and genitalia were not remarkable.

Neuropathological Findings

When the skull was opened a small amount of blood (not measured) escaped from the epidural space. Approximately 90 c.c. of dark red, clotted blood had collected in the subdural space and had compressed the parietal and occipital lobes bilaterally. The cerebral hemispheres were enormously enlarged, whereas the brain-stem and cerebellum were of normal size. The cerebral convolutions were moderately flattened and the sulci were narrowed. The arachnoidal membrane was thin and transparent. The foramens of Magendie and Luschka were patent. There was a small amount of blood in the subarachnoid space over the cerebral hemispheres and a somewhat larger amount over the basilar surfaces of the brain.

Frontal section of the cerebral hemispheres revealed a marked symmetrical

dilatation of the lateral and 3rd ventricles. The cerebral mantle was thin and varied in thickness from 0·5 to 1 cm. This thinning of the cerebral tissue affected the white matter more than grey; in some places the thickness of the cortex was greater than that of the white matter.

Beneath the ependymal lining of the lateral ventricles and in some parts of the cerebral white matter there were numerous small hæmorrhages which ranged in size from 0·05 to 0·2 cm. There was a fenestration in the septum pellucidum which measured 3·5 cm. in diameter. The aqueduct of Sylvius was extremely narrow throughout its length and in the most caudal portion was almost obliterated for a distance of 1 mm. The 4th ventricle was normal in size and configuration. The basal ganglia were flattened in the lateral and vertical plane but were otherwise natural in appearance.

Representative microscopic sections of the brain were stained with hæmatoxylin and œsin, cresyl violet, phosphostungstic acid hæmatoxylin, Cajal silver, and Sudan II with hæmatoxylin. The entire mid-brain and upper pons were embedded in celloidin and serial sections 8 microns in thickness were prepared. This permitted complete examination of the aqueduct of Sylvius from the level of the posterior commissure to the 4th ventricle.

In microscopic sections of the cerebrum there were surprisingly few significant changes. The neurones in the cortex were properly oriented and were undiminished in number. The various cortical laminæ were unusually well defined and of relatively normal thickness. In the marginal layer of the cortex the astrocytes were increased in number and size; some of them were in clusters of two or three. A slight proliferation of astrocytes and microglia was noted in all the layers of the cortex. The only obvious abnormality of the cerebral white matter was an increased cellularity in a narrow band next to the ventricle. The majority of the cells in this region were enlarged astrocytes. In a few of the sections there were numerous fat-filled microglial phagocytes arranged in another band just external to the layer of the subependymal astrocytes. Microglial phagocytes were found in the cerebral cortex in a few places. The ependymal lining was for the most part lacking.

In sections of the thalamus and the lentricular and caudate nuclei there was a slight but definite increase in both astrocytes and microglial cells. A few microglial phagocytes containing fat were found in the internal capsule. The pons and medulla were normal except for brush-like formations of astrocytes elevating the pia. The ependymal lining of the 4th ventricle was intact. The architecture of the cerebellum was normal.

The choroid plexuses of the lateral ventricles were quite small and condensed. The epithelial cells of some of the villi were unusually flat. Brownish pigment, probably hæmosiderin, was present in the cytoplasm of a few of the epithelial cells and in macrophages between the epithelial cells and in the interstitial tissue. The same pigmentary deposits were noted in the choroid plexus of the 4th ventricle but there was no flattening of the epithelial cells.

The pia and arachnoid were not remarkable except for moderate numbers of macrophages containing hæmosiderin.

In sections of the mid-brain the only important changes were in the aqueduct and the peri-aqueductual grey matter. The cerebral peduncles, red nuclei, substantia nigra and the nuclei of the 3rd and 4th cranial nerves were normally developed.

The aqueduct was patent throughout and varied in shape in the several parts. Five general regions could be distinguished. The first, or anterior portion, extended from the level of the posterior commissure to the superior border of the nuclei of the 3rd cranial nerves. Here the lumen was wedgeshaped with the apex directed ventrally, and quite narrow. The second portion, or ampulla, lay at the level of the nuclei of the 3rd nerve and was club-shaped with the narrow end directly ventrally. It was slightly larger transversely than the anterior portion.

The third, or medial portion, between the nuclei of the 3rd and 4th cranial nerves had the form of a tiny oval with the long axis in the dorsoventral plane. The fourth portion or genu, at the inferior border of the nuclei of the 4th cranial nerves and just superior to the point of transition into the 4th ventricle was largest both transversely and dorsoventrally. The outline of the lumen was shaped like a spoon with the handle directed ventrally. The fifth, or posterior portion, formed the transition into the 4th ventricle and was morphologically similar to the genu superiorly. It was quite short.

A careful study of the first four levels revealed the following specific details. The levels from which these and corresponding normal control sections[1] were taken is indicated by the horizontal lines in the sketch in fig. 4.

Anterior portion (Plate IX, fig. 2A).—The thin wedge-shaped lumen was small and measured 0·15 mm. transversely, and 1·4 mm. dorsoventrally (control 0·55 and

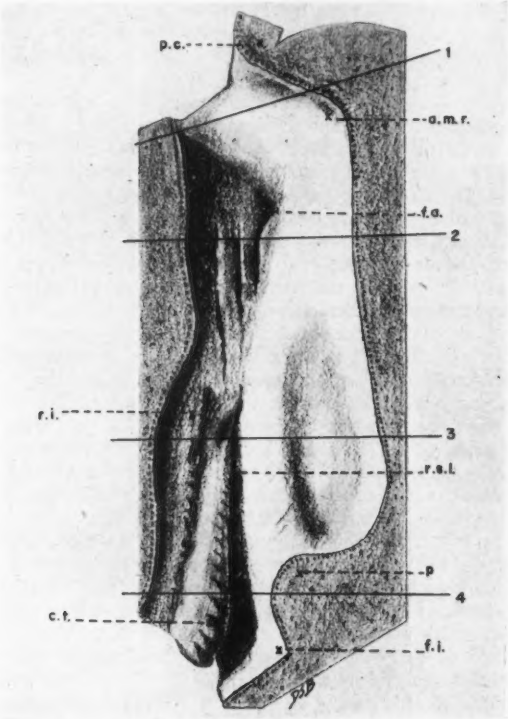

FIG. 4.—Diagram of the aqueduct of Sylvius as viewed in sagittal plane (modified from Turkewitsch). p.c.—posterior commissure; a.m.r.—anterior mesencephalic recess; f.a.—fovea ampullæ; r.i.—recessus isthmi; r.s.l.—recessus sulcus lateralis; c.t.—colliculi tegmenti; f.i.—fovea isthmi. The solid lines indicate the level of the sections of the aqueduct in figs. 2 and 3.

[1]The aqueduct of a full-term infant dying of pulmonary atelectasis at 3 days of age was fixed, embedded and sectioned in the same plane as the stenosed aqueduct and used as a control.

0·9 mm. respectively). The walls were lined with intact normal ciliated ependyma which varied in thickness from a single layer of cells in the ventral portion to a maximum of four layers in the dorsal portion. The contour of the lumen was rendered slightly irregular by the presence of several shallow parallel fissures, usually four on each side, which were oriented longitudinally along the lateral walls. The most prominent of these measured 50 microns in depth. The dorsal wall was marked by a small longitudinal crest (the dorsal crest) situated in the mid-line which is best developed in this, the anterior portion of the aqueduct (d.c. in fig. 2A). It was covered with normal ependyma, usually three cells in thickness. The sulci on either side were covered with a thin ependyma consisting of a single layer of spherical cells. A clearly demarcated rectangular sheet of small cells, the dorsal nucleus of the central grey matter of the mid-brain, streamed dorsally from this crest (d.n. in fig. 2A). It measured at this point 0·3 mm. by 1·3 mm. and was composed of very small nerve cells. Continuous with the dorsal nucleus on either side of the dorsal third of the aqueduct were the lateral nuclei of the central mesencephalic grey matter (l.n. in fig. 2A). Their composition was similar to that of the dorsal nucleus, and they were more prominent inferiorly in this portion. No abnormalities were seen in the subependymal region.

Ampulla (fig. 2B).—The lumen here measured 0·25 mm. transversely and 1·3 mm. dorsoventrally (control 1 mm. and 1·25 mm. respectively). The ependyma was intact, and varied in thickness from 1 to 4 cell layers as in the anterior portion. The lateral fissures were deeper than in the anterior portion (0·1 mm.) and some were branched. The deepest corresponded to the fovea ampullæ (f.a. in fig. 4). The dorsal crest had disappeared but the ependyma on either side of the mid-line had the same appearance as in the anterior portion. On one side of the dorsal wall a group of ependymal cells had almost completely separated from the rest of the ependymal lining. In the median raphé on either side of the mid-line were clusters and rosettes of ependymal cells. Those nearest the aqueduct were identical to the aqueductal ependyma and formed tiny tubules which did not connect with the aqueduct. The more dorsal clumps, though easily recognizable as ependymal cells stained lighter and formed less discrete tubules. They had some resemblance to the glial cells forming the rest of the median raphé. All glial elements were represented, astrocytes being predominant, but their numbers were not markedly greater than in the other portions of the central mesencephalic grey matter. The subependymal regions were otherwise not remarkable. The lateral nuclei of the central mesencephalic grey matter had almost disappeared.

Medial portion (Plate X, fig. 3A).—Here the lumen of the aqueduct was smaller than at any other level measuring 0·2 mm. in transverse and 0·7 mm. in dorsoventral diameters (control 1·05 mm. and 1·2 mm. respectively). The shape was that of a tiny oval with long axis in the dorsoventral plane. The cross section area was approximately one-fourth that of the largest or medial portion. The ventral sulcus at this level was small, measuring 0·3 mm. in depth (v.s. in fig. 3A). The lateral walls were marked on either side by four parallel longitudinal fissures, the deepest, the recess of the lateral sulcus (r.s.l. in fig. 3A). The dorsal wall presented an appearance unique to this level. A deep (0·3 mm.) branched sulcus extended dorsally in the mid-line (d.s. in fig. 3A). The ciliated ependymal lining was intact throughout and was thickest in the dorsal and ventral sulci. Adjacent to the tip of the dorsal median sulcus there was a collection of ependymal rosettes and clumps in the shape of an inverted "T". These cells were identical to those lining the aqueduct, were ciliated and had heavy glial fibrils. The latter radiated away from the canaliculi which were formed by these cells. Between them were scattered ependymal cells some single and others in small groups. A few microglial cells and astrocytes were formed amongst these ependymal cells.

Genu (fig. 3B).—The lumen here measured 0·7 mm. transversely, 2·1 mm. dorsoventrally (control 1 mm. and 2·7 mm. respectively) and was partially filled

PLATE IX

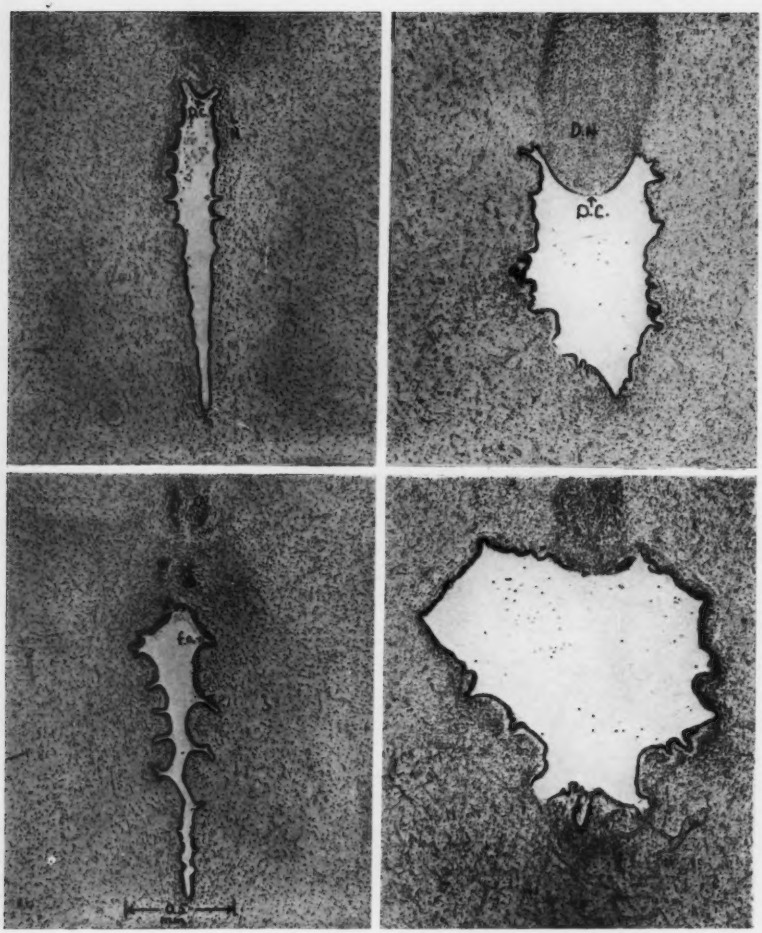

FIG. 2A.—Anterior part of the aqueduct (level 1 in fig. 4) from the case of hydrocephalus on the left and the control on the right. D.N.—dorsal nucleus; D.C. —dorsal crest; L.N.—lateral nucleus. Thionine stain. ×38.

FIG. 2B.—Ampulla of aqueduct (level 2 in fig. 4) from the case of hydrocephalus on left and the control on the right. f.a. fovea ampullæ. Thionine stain. ×38.

To illustrate article by Donald S. Bickers, M.D., and Raymond D. Adams, M.D.

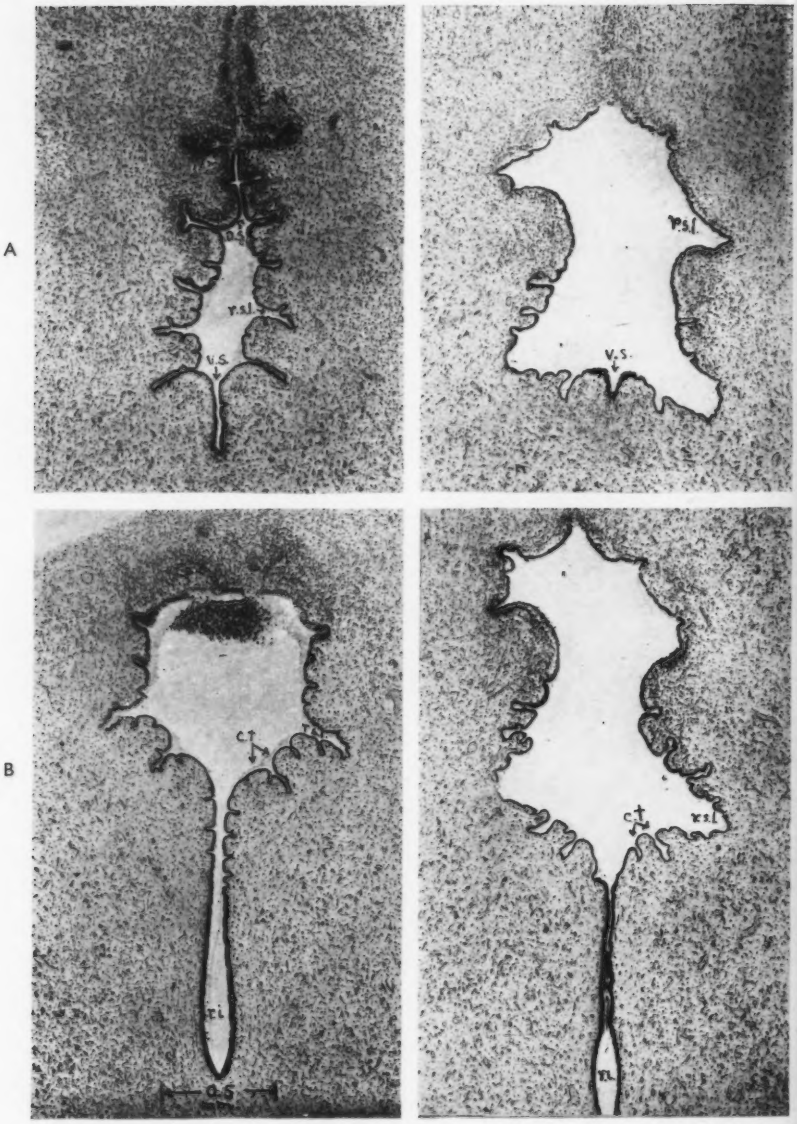

FIG. 3A.—Medial part of the aqueduct (level 3 in fig. 4) from the case of hydrocephalus on the left and the control on the right. D.S.—dorsal sulcus; r.s.l.—recessus sulcus lateralis; v.s.—ventral sulcus; e.n.—ependymal cell nests. Thionine stain. ×38.

FIG. 3B.—Genu of aqueduct (level 4 in fig. 4) from the case of hydrocephalus on the left and control on the right. c.t.—colliculi tegmenti; r.i.—recessus isthmi. Thionine stain. ×38.

To illustrate article by Donald S. Bickers, M.D., and Raymond D. Adams, M.D.

with an aggregation of macrophages which contained brownish granules. The ependymal lining was intact, and the two segments where the ependyma was thin appeared again on either side of the mid-line in the dorsal wall. The ependyma was thickest near the junction of the dorsal and lateral walls. The lateral fissures were deeper and tended more to arborization. On either lateral wall there was a deep (2·5 mm.) lateral sulcus (r.s.l. in fig. 3B). Ventral to these sulci the lateral walls bulged symmetrically inward and almost touched. These protuberances represented the tegmental colliculi of the aqueduct (c.t. in fig. 3B). A narrow vertical slit formed by progressive deeping of the ventral sulcus, the recessus isthmi (r.i. in fig. 3B), separated the colliculi. In the dorsal wall at the points of alteration of the ependymal wall, there were a few small clusters of glial cells. These did not protrude into the lumen, and were surrounded dorsally by a continuous palisade of ependymal cells. Several clumps and rosettes of ependymal cells were seen dorsal to the palisaded ependymal region on either side of the mid-line. There were no abnormalities in the remaining subependymal regions.

COMMENT.—In this case the chief points of pathological interest were limited to the intracranial structures. The brain had the characteristic appearance of quite advanced hydrocephalus. The thinning of the cerebral white matter and the much less severe thinning of the cortex were due to distension of the lateral ventricles. Unquestionably there was hydrocephalic atrophy of the brain but, as is usually the case, its extent was difficult to judge at autopsy since a great expansion of the cerebral hemispheres was coincident to compression of the cerebral white matter. The histopathological changes in the cerebrum, consisting of destruction of ependyma, subependymal gliosis, presence of foci of microglial phagocytes in some parts of the white matter and the relative preservation of the cortex are the usual findings of congenital hydrocephalus (cf. Penfield and Elvidge [33]).

The marked dilatation of the lateral and 3rd ventricles was evidently due to the stenosis of the aqueduct of Sylvius. The 4th ventricle was normal in size, the foramens of Magendie and Luschka were patent and the meninges and subarachnoid spaces were natural in appearance. These findings tended to exclude other possible mechanisms of hydrocephalus. The aqueduct was not completely occluded at any point but was definitely narrowed particularly at the medial portion. This is borne out by comparison with the normal measurements in the literature (cf. Turkewitsch) and as already indicated with our own control aqueduct. Presumably the narrowed aqueduct was functionally incompetent to permit the escape of cerebrospinal fluid from the 3rd and lateral ventricles to the 4th ventricle.

The epidural and subdural hæmatomas and the subarachnoid hæmorrhage were surely the result of the ventriculostomy performed during parturition or of birth trauma. The colour of the blood in the hæmatomas, the hæmosiderin in macrophages in the choroid plexuses, the aqueduct and the subarachnoid space would indicate that the hæmorrhage had occurred some seven to ten days before death. The

multiple small subependymal hæmorrhages were probably due to rapid decompression of the over-distended ventricles. The flattening of the epithelium of choroid plexuses of the lateral and 3rd ventricles and the fenestration of the septum pellucidum were secondary pressure effects.

Discussion

In searching for cases of congenital hydrocephalus due to aqueductal stenosis which were morphologically similar to ours, one of us (D. B.) reviewed all available published accounts of this disease. We were unable to find any other pathologically verified cases in which the disease had occurred in more than one member of a family or in successive generations, except possibly the case described by Ford. Nevertheless several rather interesting facts were discovered.

To the best of our knowledge the first recorded example of hydrocephalus caused by stenosis of the sylvian aqueduct was described by Hilton [17] in 1863. This case, a female dying at the age of 7 months came under his observation in 1847. Other early reports now mainly of historical interest are those of Bourneville and Noir [4] who in 1900 presented the case of a 9-year-old boy with hydrocephalus from the age of 7 months and Touche [44] who in 1902 wrote of a similar case occurring in a 29-year-old woman with symptoms of four years' duration. Oppenheim [27] in 1900 described a case in which the aqueduct consisted of two small canals each completely lined by ependymal cells and separated by a bridge of glial tissue. He regarded this as a reduplication of the aqueduct. There was no mention of hydrocephalus. In all of these cases the narrowing of the aqueduct was demonstrated grossly but the description of the pathology was so meagre that the cause of the stenosis could not be ascertained.

The first adequate account of the microscopic pathology can be found in the writings of Spiller [39] in 1902. In 1 of 2 cases of internal hydrocephalus which he studied there was a gliosis beneath the ependyma of the narrowed aqueduct. Later in 1907 in collaboration wtih Allen [41] he described the first case of aqueductal stenosis in which the hydrocephalus had developed during fœtal life.

Appearing sporadically from 1908 until the present there have been case reports and general reviews of the subject. These articles purport to show that aqueductal stenosis is a natural phenomenon, occurring not too infrequently and resulting in hydrocephalus which becomes manifest either before or after birth. To date there are 43 pathologically verified cases sufficiently described to permit classification in which intrinsic, non-neoplastic stenosis of the aqueduct was demonstrated to be the cause of obstructive hydrocephalus. 24 of these cases, including ours, were

congenital. Cases in the congenital group have been described by Couceiro [6], Dandy and Blackfan [10], Dandy [9], Dijkstra [12], de Lange [21], Parker and Kernohan [30], Roback and Gerstle [32], Schlapp and Gere [35], Shrycock and Ashley [37], Spiller and Allen [41], and Watson [48]. Those in the "acquired" or post-natal group with stenosis of the aqueduct have been described by Beriel [3], Christensen [5], Dahl and Harbitz [7], Dijkstra [12], Glettenberg [14], Globus and Bergman [15], Guthrie [16], Kernohan [19], Orton [28], Parker and Kernohan [30], Shelden, Parker and Kernohan [36], Sneeden [38], and Spiller [39]. In Pennybacker's report [31] there are 18 cases which apparently belong to this group but the descriptions are too meagre to justify their inclusion. These 43 cases are summarized at the end of this report.

The mode of development of aqueductal stenosis has been the subject of much speculation. Two hypotheses have received serious consideration. The oldest of these proposes that an intra-uterine infection either induces chronic inflammatory reaction around the aqueduct with consequent gliosis and constriction, or so damages the primitive mesencephalic anlage that development is retarded. D'Astros [2] in 1898 (quoted by Roback and Gerstle) first advanced this idea of a toxin or infection in embryonic life and Guthrie [16], probably influenced by the occurrence of syphilis or tuberculosis in 7 of his 8 cases, also favoured intra-uterine infection as the main ætiologic factor. Dandy and Blackfan [11] adhered to this concept. Schlapp and Gere [35] modified the view somewhat in that they believed an infection had acted on embryologically defective tissue.

The second hypothesis, introduced by Spiller [40], was that the aqueduct of Sylvius underwent involution much like the central canal of the spinal cord which usually becomes closed between the ninth and seventeenth years of life. He cited the common origin of these two structures from the primitive neural tube as an explanation of their similar behaviour. In his report on aqueductal stenosis accompanied by heterotopia, and later in communications with Shelden and Parker [30, 36], Kernohan supported this notion. Orton [29] accepted this hypothesis and stressed the importance of a "heavy glial framework." Other adherents to this view were de Lange [21], Marburg [25], Dijkstra [12], Roback and Gerstle [32], Couceiro [6], Shrycock and Ashley [37].

Stookey and Scarff [43] and Dahl and Harbitz [7] maintain that both hypotheses are tenable. They point out that in some cases an intra-uterine infection has been the cause of aqueductal stenosis and in others a congenital anomaly existed. We concur with this viewpoint. To us there seems to be little doubt that chronic infection, usually both meningitis and ependymitis, can produce a functionally significant aqueductal narrowing. The aqueduct is peculiarly vulnerable to such narrowing

[*Continued on page* 259.

TABLE I.—CONGENITAL HYDROCEPHALUS DUE TO STENOSIS OF THE AQUEDUCT OF SYLVIUS

	Author	*Case No.*	*Sex*	*Age at onset*	*Age at death*	*Pathological findings in aqueduct and meninges*	*Other anomalies*
1	Couceiro, 1940	2	F	Birth	1 1/2 yrs.	Stenosis anterior part. Gliosis, ependymal rosettes, clumps. Normal meninges.	0
2	Idem	3	M	Birth	6 mos.	Stenosis inferior part. No periaqueductal changes or ependymal clumps or rosettes. Normal meninges	0
3	Dandy and Blackfan, 1914	2		Birth		Atresia by subependymal gliosis in upper part., ependymal-lined tubules below. ? Normal meninges	Myelomeningocœle
4	Idem	3		Birth		No trace of aqueduct visible. ? Normal meninges	0
5	Dijkstra, 1930	3		Birth	3 1/2 wks.	Aqueduct obliterated by glial nodules. Ependymitis. Acute leptomeningitis	0
6	de Lange, 1929	1		Birth	2yrs. 9 mos.	Stenosis inferior part aqueduct. No ependymal or subependymal change. Acute purulent meningitis	Spina bifida with hydromyelia
7	Idem	4	F	Birth	23 mos.	Aqueduct closed by glial membrane surrounded by ependymal rosettes. General ependymitis. Basilar meningitis ? luetic	Bilateral coloboma of choroid
8	Idem, 1936	1		Birth	1 yr. 1 wk.	Interior portion closed by glial membrane partially covered with ependyma. Accessory tubules, rosettes, clumps. Some subependymal gliosis. Acute purulent leptomeningitis.	Spina bifida
9	Parker and Kernohan, 1933	3	M	2 mos.	6 yrs.	Subependymal gliosis with ependymal-lined tubules. No inflammatory changes in ependyma. Normal meninges.	0
10	Roback and Gerstle	1	M	Birth	3 days	Aqueduct narrowed by nodules of sub-ependymal glia. Ependymitis at inferior colliculi. ? Normal meninges	Spina bifida ? myelomeningocœle
11	Idem	2	M	6 wks.	3 1/2 mos.	Atresia of inferior portion of aqueduct by subependymal gliosis. Tubules with intact ependymal lining present. Normal meninges	Clubfoot
12	Idem	3	M	Birth	12 days	Atresia of aqueduct at superior colliculi by glia. Narrowed at other points with intact ependyma. Normal meninges.	Spina bifida with meningocœle
13	Idem	4	F	Birth	4 mos. 3 wks.	Atresia of aqueduct by subependymal gliosis and fibrous connective tissue proliferation at superior colliculi. Normal meninges.	Spina bifida with meningomyelocœle
14	Idem	5	F	2 wks.	6 wks.	Stenosis by subependymal gliosis and ependymitis. Chronic streptococcal meningitis	Spina bifida with myelomeningocœle
15	Idem	6	M	Birth	3 days	Stenosis by subependymal gliosis, ependymitis. Normal meninges	Webbed and misdirected toes

TABLE I.—*Continued*

Author	*Case No.*	*Sex*	*Age at onset*	*Age at death*	*Pathological findings in aqueduct and meninges*	*Other anomalies*
16 Schlapp and Gere, 1917	1	M	Birth	3 1/2 yrs.	Proliferation of ependyma, subependymal gliosis with complete atresia. Ependymal rosettes and clumps in raphé. Normal meninges	0
17 Idem	2	M	1 mo.	5 1/2 mos.	Complete atresia of mid-portion of aqueduct with subependymal gliosis, rupture of ependyma. Ependymal rosettes and clumps. Normal meninges ,	0
18 Idem	3	F	Birth	2 1/2 yrs.	Complete atresia of aqueduct, subependymal gliosis. Normal ependyma in dilated anterior portion. Normal meninges	Absent corpus callosum and pyramidal tracts
19 Idem	7		Birth	Stillborn	Marked stenosis of aqueduct with subependymal gliosis. Normal meninges	
20 Shrycock and Ashley, 1942	1	M	Birth	4 mos.	Almost complete atresia with subependymal gliosis, level of superior colliculus. Ependyma almost intact. Normal meninges	Hydranencephalocœle
21 Spiller and Allen, 1907	1	F	Birth	62 yr.	Marked stenosis of aqueduct throughout with intact ependyma and slight subependymal gliosis. Pin-point size. Normal meninges	0
22 Watson, 1944	1		Birth	9 days	Aqueduct ends in blind sac, lined with normal ependyma. Normal meninges.	Anencephaly. Diencephalon, basal ganglia choroid plexuses intact.
23 Idem	2		Birth	18 days	Aqueduct not seen. Normal meninges	Anencephaly. Thin allocortex of temporal and parietal lobes present. No diencephalon, midbrain poorly formed. Basal ganglia, choroid plexuses present
24 Bickers and Adams, 1949	1	M	Birth	13 days	Stenosis throughout entire aqueduct. No subependymal gliosis. Ependymal rosettes and clumps in raphé. Normal meninges except hæmosiderin from ventriculostomy	0

TABLE II.—ACQUIRED (POSTNATAL) HYDROCEPHALUS DUE TO STENOSIS OF THE AQUEDUCT OF SYLVIUS

Author	*Case No.*	*Sex*	*Age at onset*	*Age at death*	*Pathological findings in aqueduct and meninges*	*Other abnormalities*
1 Christensen, 1942	2	M	24 yrs.	24 yrs.	Ependymitis and subependymal gliosis occluding aqueduct (fibrillary astrocytes). Meninges normal	0
2 Idem	3	F	34 yrs.	38 yrs.	Ependymitis and subependymal gliosis occluding aqueduct (fibrillary astrocytes). Meninges normal	0

TABLE II. (*codtd.*)—ACQUIRED (POSTNATAL) HYDROCEPHALUS DUE TO STENOSIS OF THE AQUEDUCT OF SYLVIUS

Author	*Case No.*	*Sex*	*Age at onset*	*Age at death*	*Pathological findings in aqueduct and meninges*	*Other abnormalities*
3 Dahl and Harbitz, 1938	3	M	16 yrs.	21 yrs.	Ependymitis with cystic degeneration of glial nodules. Subependymal gliosis, near complete occlusion of aqueduct. Meninges normal	0
4 Dijkstra, 1930	1		16 yrs.	16 yrs.	Stenosis of aqueduct, with subependymal gliosis, ependymal cell nests, ependymitis. No ependymal changes elsewhere. Meninges normal	0
5 Idem	2	F	26 yrs.	27 yrs.	Marked aqueductal stenosis by ependymitis, subependymal gliosis, glial trabeculations. Ependymal cell nests. Meninges normal	0
6 Glettenberg, 1936	1	F	35 yrs.	35 yrs.	Aqueduct occluded by constricting peri-aqueductal subependymal gliosis composed of glial fibrils and small glial cells. Meninges normal	0
7 Idem	2	M	7 yrs.	13 yrs.	Aqueduct stenosed by subependymal gliosis similar to Case 1. Meninges normal	0
8 Idem	3	M	10 yrs.	41 yrs.	Marked stenosis by subependymal gliosis similar to Case 1. Meninges normal	0
9 Globus and Bergman, 1946	1	F	46 yrs.	49 yrs.	Stenosis of posterior third of aqueduct with subependymal gliosis. Ependymal-lined canaliculi. Meninges normal	0
10 Idem	2	M	20 yrs.	21 yrs.	Stenosis of anterior third of aqueduct with subependymal cell nests. Some perivascular lymphocytic cuffing. Meninges not described	0
11 Idem	3	M	35 yrs.	38 yrs.	Atresia of anterior third of aqueduct by glial membrane. Ependymitis and subependymal gliosis. Ependymal cell nests. Meninges not described	Porencephaly of right frontal lobe
12 Kernohan, 1930	1	F	?	3 yrs.	Complete occlusion of aqueduct at two points by a few glial nodules. Most ependyma normal. Localised subependymal glial reaction predominantly of microglia. Meninges slightly thickened, no perivascular cuffing. Small accessory canaliculi lined with normal ependyma	Heterotopia in subependymal regions of lat. ventricles. Cerebral cortex poorly developed, contained heterotopic nodules
13 Orton, 1931	1	F	17 yrs.	17 yrs.	Marked stenosis of aqueduct by ependymitis and subependymal gliosis. Ependymal rosettes. Gliosis seen in periphery of pons, medulla, spinal cord	0
14 Parker and Kernohan, 1933	1	F	4 yrs.	23 yrs.	Stenosis of aqueduct by ependymitis, subependymal gliosis. Ependymitis in other ventricles. Meninges normal	0

TABLE II.—*Continued*

Author	*Case No.*	*Sex*	*Age at onset*	*Age at death*	*Pathological findings in aqueduct and meninges*	*Other abnormalities*
15 Idem	4	F	3 yrs.	11 yrs.	Stenosed aqueduct lined with normal ependyma throughout. No ependymitis or subependymal gliosis. Slight thickening of basilar meninges. No evidence of inflammatory process	0
16 Sneeden and Larson, 1930	1	M	2 1/2	3 1/2	Aqueduct narrowed for distance of 1 cm. by subependymal gliosis and ependymitis. Cystic degeneration of some glial nodules. Meninges normal	0
17 Shelden, Parker and Kernohan, 1930	1	F	6 yrs.	11 yrs.	Aqueduct narrowed to slit by ependymitis and subependymal gliosis. Ependymal nests and rosettes. Meninges normal	Myelomeningocœle at T_7
18 Idem	2	M	4 yrs.	4 yrs.	Posterior third of aqueduct almost obliterated by subependymal gliosis. Many ependymal tubules. No ependymal granulations. Glial proliferation primarily fibrillary. Meninges normal	0
19 Spiller, 1902	2	M	Childhood	19 yrs.	Aqueduct almost occluded by ependymitis (glial nodules). Subependymal gliosis and ependymal rosettes and nests. Meninges normal	0

because of its length and small diameter. This form of the disease can be recognized by the presence of inflammatory cells in the perivascular spaces of subependymal vessels and/or by reactive changes in microglial cells and astrocytes in the subependymal tissue. It seems equally certain that in cases dying in infancy where the aqueduct is stenosed without such histopathological changes a developmental anomaly has existed. Obviously in some cases the conditions may coexist, i.e. meningitis and ependymitis superimposed on an aqueduct which has not developed adequately.

The particular merit of the rather remarkable genealogy reported here is that it offers substantial evidence that aqueductal stenosis can be an hereditary disease. The pedigree is so short that it is impossible to determine whether the dominance in males is due to the presence of a sex-linked factor or to a difference in penetrance of the affected genes. Admittedly, one cannot be sure that the other 6 cases of congenital hydrocephalus in this family had aqueductal stenosis since no other post-mortem examinations were made, but their clinical similarity to the autopsied case makes it more than probable.

The actual developmental mechanism whereby the aqueduct stenosis is produced is still a matter of conjecture. From the excellent anatomical studies by Turkewitsch [45, 46, 47] of the aqueduct of human embryos of different ages (2·5 cm. to 35 cm. crown-rump length) and in an adult, two salient facts emerge. First, there is an absolute as well as a relative decrease in the size of the aqueductal lumen which occurs progressively from the second fœtal month to the time of birth. This process is most marked in the medial portion and the ampulla. The other parts of the aqueduct, although retaining approximately the same diameters all through fœtal life, also decrease in cross section area but to a lesser degree. Secondly, there is an increase in length of the aqueduct from 3·5 mm. in the 2·5 cm. embryo to 7 mm. in the 35 cm. embryo. In post-natal life the aqueduct gradually enlarges in all dimensions reaching its maximum in the adult. As with many growth processes it would seem that the narrowing which occurs normally *in utero* may be excessive and even continue into post-natal life (cf. Spiller [39] and Kernohan [19]) or the post-natal enlargement is retarded. Thus physiological inadequacy may become manifest either during fœtal life or in childhood and adolescence. This hypothesis received added support from our case where the greatest degree of stenosis was in the dorsal half of the aqueduct, i.e. that portion dorsal to the lateral sulci. The anterior and posterior mesencephalic recesses and most of the dorsal longitudinal sulcus were apparently obliterated by fusion of the dorsolateral walls.

There was nothing in our case to indicate that the aqueduct was crowded by the faulty migration of primitive neuroblasts and spongioblasts as has been stressed by Roback and Gerstle [32] because the nuclei in the tegmentum and base of the mid-brain and upper pons appeared to be normally disposed. Nor was there astrocytic hyperplasia or other histologic evidence of an inflammatory process. The ependymal rosettes near the aqueduct are of interest and are believed by some workers to indicate a premature closure of the neural tube. However, since ependymal formations are commonly found in the raphé of the mid-brain, the lateral recess of the medulla and near the central canal of the spinal cord in normal cases, their exact significance must remain in doubt.

One additional point, well exemplified by our case is that hydrocephalus may result from a critical narrowing of the aqueduct of Sylvius. The aqueduct is functionally incompetent and cerebrospinal fluid is formed more rapidly than it can escape from the 3rd ventricle. In all of the cases of chronic hydrocephalus with aqueductal obstruction a stenosis rather than occlusion has been demonstrated. We agree with Kernohan (personal communication) that complete occlusion of the aqueduct is incompatible with life.

SUMMARY

A case of congenital hydrocephalus due to aqueductal stenosis is presented. The pathological findings and the remarkable family history of similar cases occurring in 6 other males in two successive generations support the proposition that smallness of the aqueduct of Sylvius may occur as an inherited abnormality.

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Notices of Recent Publications

Epilepsies; leurs formes cliniques, leurs traitements. By L. Marchand and J. de Ajuriaguerra. Bibliothèque neuro-psychiatrique de langue française. Pp. 721. 11 illustrations. Paris: Desclèe de Brouwer et Cie. 1948. Price—not stated.

Neurologists will welcome this important monograph, which should prove a useful source-book to anyone working upon the problem of epilepsy. Furnished with many hundreds of references, it constitutes a detailed and valuable compilation. It is not altogether free from common drawbacks of all compilations, a tendency to sacrifice critical appraisal and judgment upon the altar of encyclopædic documentation. In the effort to omit nothing from the literature the personal touch inevitably suffers. The authors, Drs. Marchand and de Ajuriaguerra, believe that all epilepsies are symptomatic, and that so-called essential or idiopathic epilepsies are those where the causal brain lesions are not identified in the living subject. The monograph is divided into seven sections which deal respectively with (1) L'epilepsie convulsive; (2) l'epilepsie psychique; (3) the clinical value of electroencephalography; (4) special types of epilepsy; (5) types depending upon age; (6) types according to the course of the disease; and (7) treatment.

When such a valuable bibliography is included it is regrettable that the Harvard system of references is not utilized.

Functional Localization in the Frontal Lobes and Cerebellum. By J. F. Fulton, being the Withering Lectures in the University of Birmingham for 1948. Geoffrey Cumberlege, the Oxford University Press, 1949. Price 15s.

In these four lectures, Professor Fulton re-states his time-honoured thesis on the organization of the precentral motor cortex, discusses in the light of modern experimental research and neurosurgery the possible functions of the frontal areas in apes and man, and sums up some recent work upon topographical localization in the cerebellum.

In dealing with the precentral motor cortex, the author will be found not to have moved at all in his views since these hardened into a kind of dogmatic finality some fifteen years ago. For him the familiar cytoarchitectonic map is still the kind of mariner's chart by which the experimenter can navigate with absolute certitude that he is on his course over any individual motor cortex. The recent critical review of cortical cytoarchitectonic studies by Lashley and Clark, so shattering, one would have thought, to any who holds this naïve view, has left him unmoved and he does not even refer to it.

He still maintains that pyramidal lesions produce negative results only, and although his bibliography gives the reference to the 1947 paper of Denny-Brown and Botterell—at the original presentation of which he was in the chair, — in which the authors find that "hemiplegic spasticity" is indeed a "pyramidal sign", and that "spasticity accompanies the paralytic manifestations of all area 4 lesions"—he still holds, with a doggedness that must command our admiration, that pyramidal lesions produce a paresis that is flaccid.

He deprecates "philosophic reflection" as an intellectual weapon in the determination of the functions of the cortex, giving experiment as his alternative. Yet surely these two modes of activity are not alternatives, but complementary activities, and when the experimenter proves unwilling to reflect philosophically upon his own observations, surely his readers may be permitted to do so.

In the succeeding chapters in which the author is not swayed by his devotion to the conception of the motor cortex as a mosaic, with each piece representing a "muscle", his thought runs more easily and is less trammelled. Here the reader will find a more balanced survey of the anatomical and physiological significance of modern surgical truncations of the frontal poles, and his final chapter gives a useful summary of certain aspects of cerebellar organization.

These lectures are not easy reading, but they have the liveliness we have learned to expect from their distinguished author, and they are abundantly and clearly illustrated. The book will set the neurological student with a severe challenge to his critical faculty, and this, when accepted, is a valuable and essential part of training.

ASSOCIATION OF BRITISH NEUROLOGISTS.

President: Professor E. D. Adrian, *O.M.*

The Twelth Annual Meeting was held at the National Hospital, Queen Square, London, W.C.1, on Friday, May 27, 1949, and Saturday, May 28, 1949.

Scientific Business

Friday afternoon, May 27.

1. J. D. Spillane: "Some observations on Cushing's Syndrome." (A)
2. G. Smythe: "Tuberculoma of the Spinal Cord." (B)
3. R. S. Allison: "Disseminated Sclerosis: Survival for long Periods." (C)

The following demonstrations were held:

1. J. A. V. Bates: "A Technique for Studying Cortical Activity in Voluntary Movement."
2. Marion Smith and Peter Nathan: "A Brain from a Man of Normal Mentality Showing Gross Abnormalities in the Telencephalon."
3. Marion Smith and Peter Nathan: "Observations from Work in Progress on the Pain Pathway in the Spino-Thalamic Tract."
4. Alick Elithorn and M. A. Crosskey: "Vasomotor Activity: Response to Unilateral Stimuli."
5. P. Merton: "A Myographic Investigation of the Ankle Jerk."
6. J. G. Greenfield: (i) "Subacute Inclusion Encephalitis"; (with H. Garland) (ii) "Subacute Pan Poliomyelitis."
7. W. Blackwood: "Pathology of a Case of Hereditary Perforating Ulcers of the Feet."
8. W. A. Cobb: "Technique of Electromyography."
9. Hugh Davies: "Neuro-radiological Demonstrations."

Saturday morning, May 28.

1. S. P. Meadows: "Pressure Optic Atrophy." (D)
2. Fergus R. Ferguson and John Marshall (introduced): "Low Cerebrospinal Fluid Pressure and the Occurrence of Post Lumber Puncture Headache." (E)
3. Denis Williams: "Thalamic Discharges Accompanying Limitation of Voluntary Movement." (F)
4. Macdonald Critchley: "The Phenomenon of Tactile Repression (Extinction) in Parietal Lesions." (G)
5. W. Ritchie Russell: "Traumatic Epilepsy—the Type of Fit Compared to the Site of Wounding." (H)

Macdonald Critchley,
Honorary Secretary.